코로나 19 변이주 특성 및 항원성 변화가 면역 회피에 미치는 영향

고려대학교 의과대학 미생물학교실
고려대학교 백신혁신 센터

김기순

2023년 4월 8일-대한결핵호흡기학회 (여수 엑스포)

고려대학교 의과대학
Korea University College of Medicine

VIC-K
고려대학교 의과대학
백신혁신센터

고려대학교 의과대학
Korea University College of Medicine

JIM Journal of Internal Medicine
Founded in 1863

Review | Free Access

COVID-19 diagnosis and management: a comprehensive review

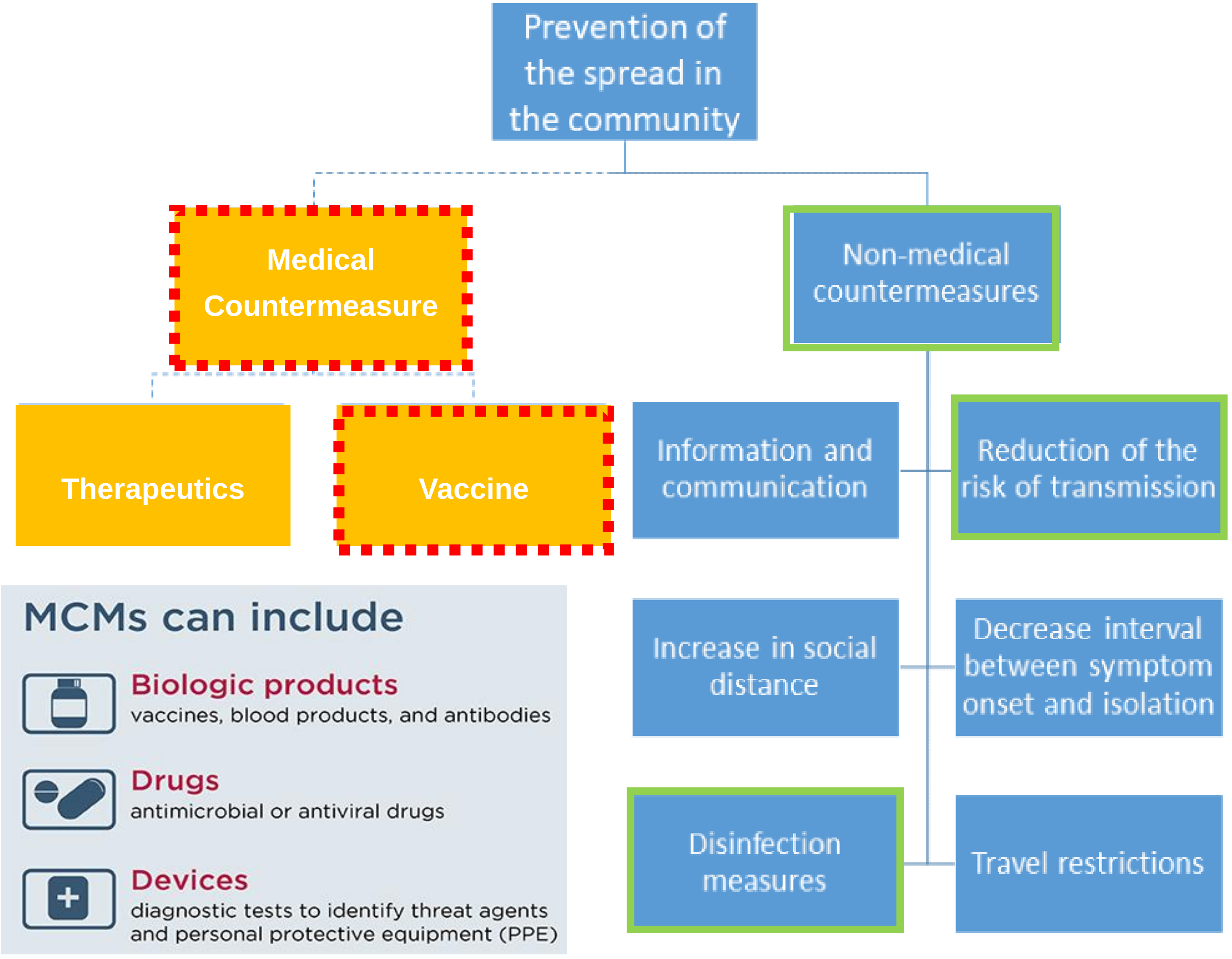
Giuseppe Pascarella, Alessandro Strumia, Chiara Piliego, Federica Bruno, Romualdo Del Buono, Fabio Costa, Simone Scarlata, Felice Eugenio Agrò

First published: 29 April 2020 | https://doi.org/10.1111/joim.13091 | Citations: 591

1. Isolation
2. Dx
3. Therapy
4. Vaccination
5. Medical care for Life support

감염 예방과 관리 (방역) 시 3가지 기본 접근법

- **예방접종,** 항균제/항바이러스제 치료 등에 의한 감염증의 예방과 증상의 경감
- 병원체의 병원성을 파괴하거나 관리
- 감염원의 제거나 전파경로 차단

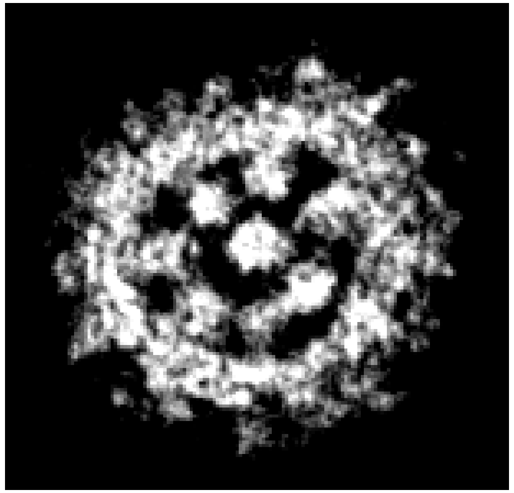


BEYOND CONTAINMENT: HEALTH SYSTEMS RESPONSES TO COVID 19 IN THE OECD © OECD 2020

Molecular evolution of RNA viruses

Genotype → Phenotype

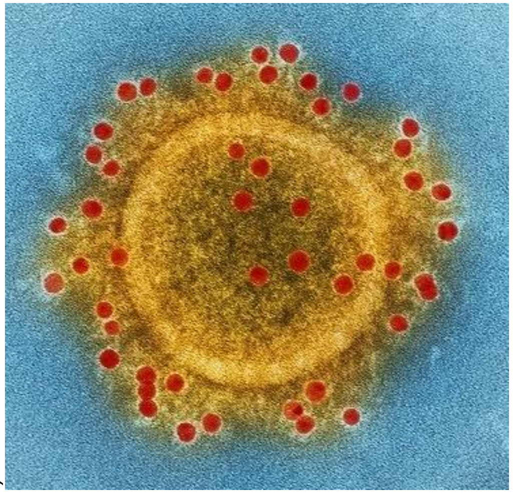
Influenza



(Noda et al., *Nature Communications* 2014)

Antigenic drift

Antigenic shift



(©NIAID from *Proteogenix Science*)

Corona

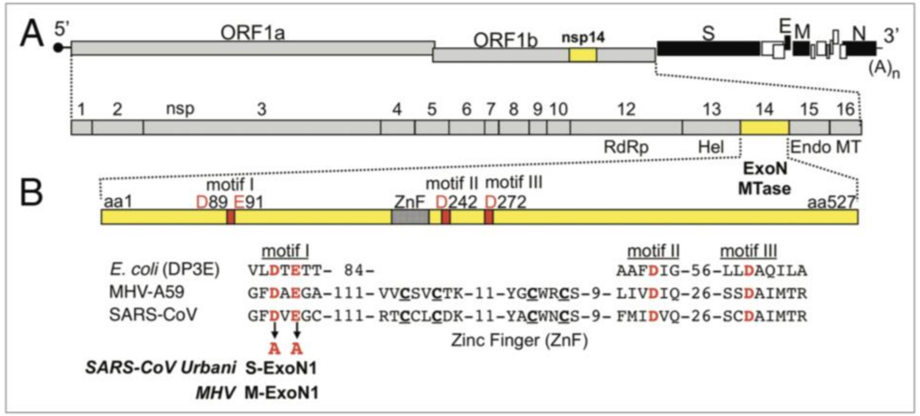
Antigenic drift

D-E--D-D motif
: conserved for the exonuclease activity

Genetic recombination

No *proofreading* mechanisms

Error-prone RNA polymerase in RNA viruses



↓

Less mutations than other RNA viruses

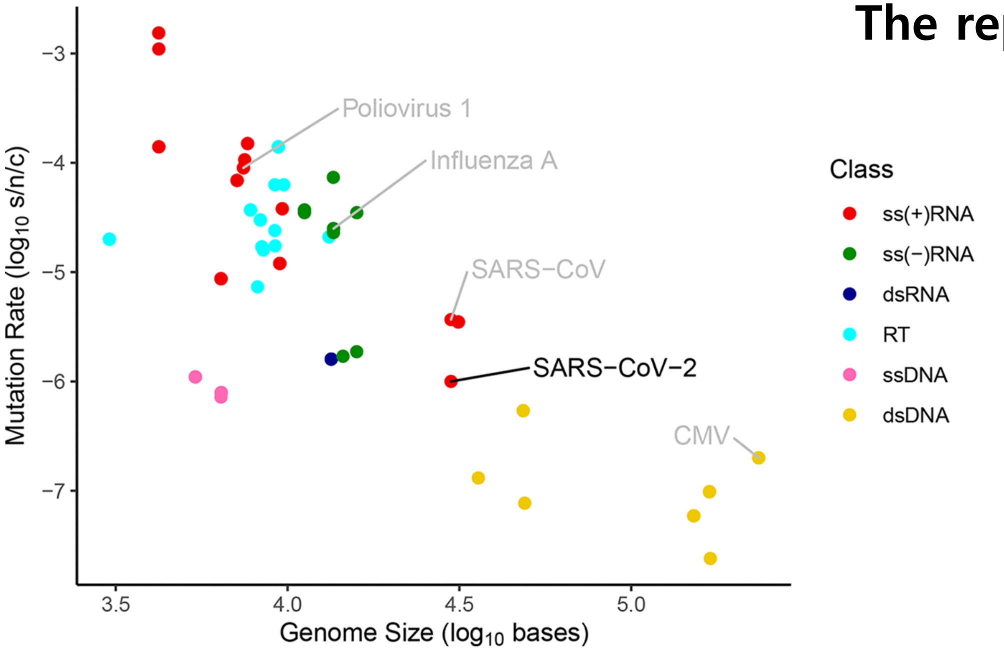
Mutation of RNA viruses

고려대학교 의과대학
Korea University College of Medicine

- 여느 바이러스와 마찬가지로 SARS-CoV-2도 대유행이 시작된 이후 계속해서 돌연변이를 일으키고 있음
- 2020년 11월 이후 영국으로 부터 감염력이 높아진 (감염력 변화와 관계있는) 바이러스 변이주 발생
- 2021년 11월 남아공으로부터 기존의 변이 pattern과는 다른 Omicron 변이주 및 하위변이 출현
- 현재 거의 모든 나라에서 Omicron이 우세

➔ **갑자기 바이러스가 놀라운 속도로 변하고 있는 것 같았으나 SARS-CoV-2는 실제로 돌연변이 속도가 높아지지 않았음**

- 대신 전 세계 인구를 대상으로 감염 기회가 높아지면서 복제시 변이가 생길 수 있는 chance가 많아짐
- 바이러스가 시간이 지남에 따라 변하는 것은 예견되어 왔음



The reported mutation rate for SARS-CoV-2 is typical for coronaviruses.

➔ 10^{-6} / nt^{-1} / $cycle^{-1}$ ➔ low for an ss(+)RNA virus

➔ high enough to mutate on average every amino acid in spike at least once in one patient

❖ SARS-CoV-2 spike evolution rate : 5×10^{-3}substitutions/site/year

◆ Higher than the evolution rate across the entire SARS-CoV-2 genome (1~1.6 × 10^{-3} substitutions/site/year; around 2 substitutions per genome per month) but still within the range of other betacoronaviruses

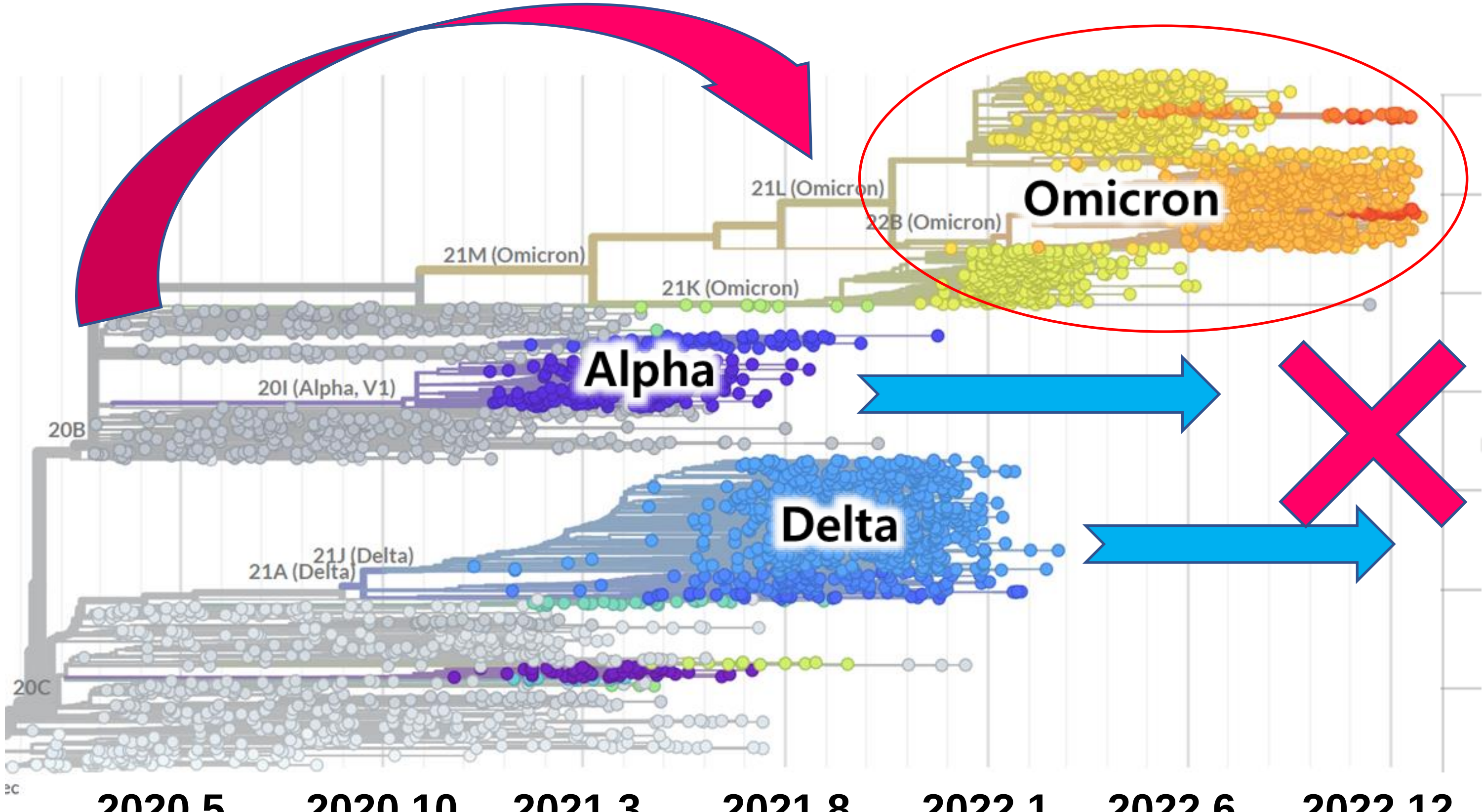
✓ 2.8-4.4 × 10^{-3} s/s/y in the IFNV-A

mSphere Vol. 6, No. 3, 2021

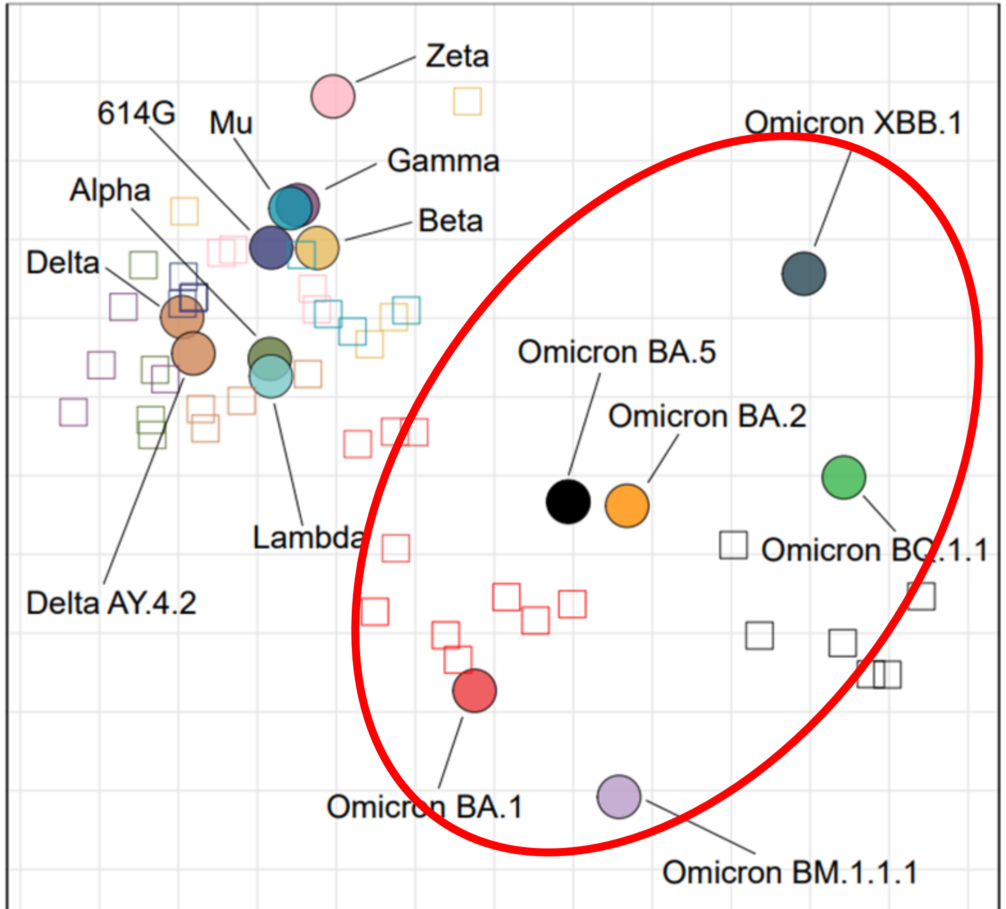
J Transl Med 21, 152 (2023).

Emergence of SARS-CoV-2 variants

- First identified in December 2019 in Wuhan, and the WHO declared a pandemic in March 2020
- 640M infected and 6.6M death in worldwide (December, 2022, WHO)
- Emergence of Omicron variants with significantly different antigenicity a year ago.



Nextstrain



Anna Z Mykytyn, the lancet microbe, (2023)

Contents lists available at ScienceDirect

Journal of Genetics and Genomics

Journal homepage: www.journals.elsevier.com/journal-of-genetics-and-genomics/

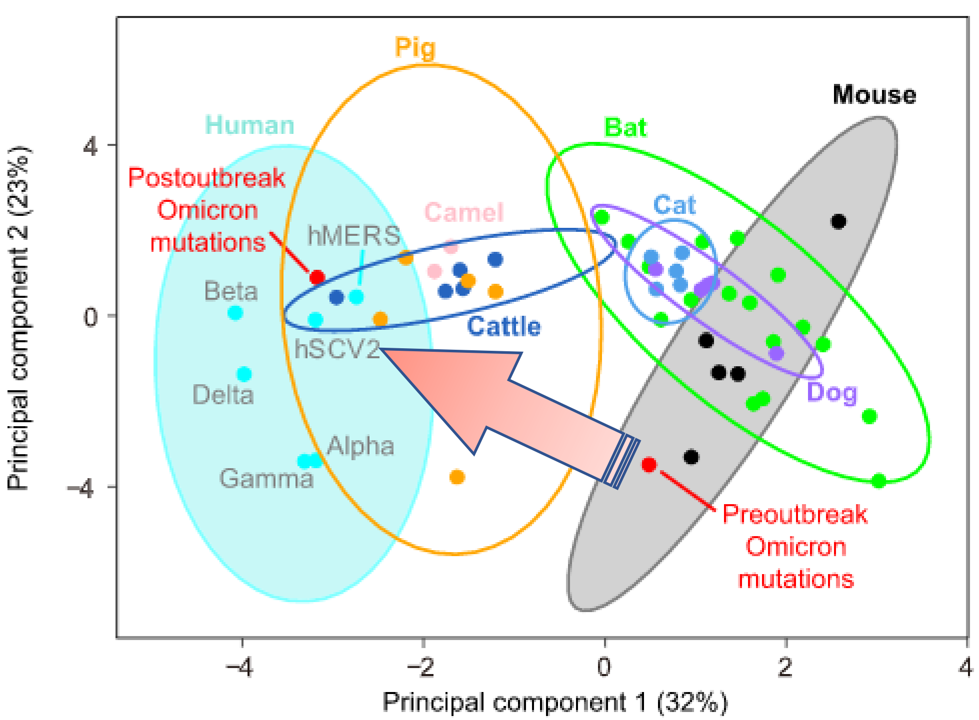
고려대학교 의과대학
Korea University College of Medicine

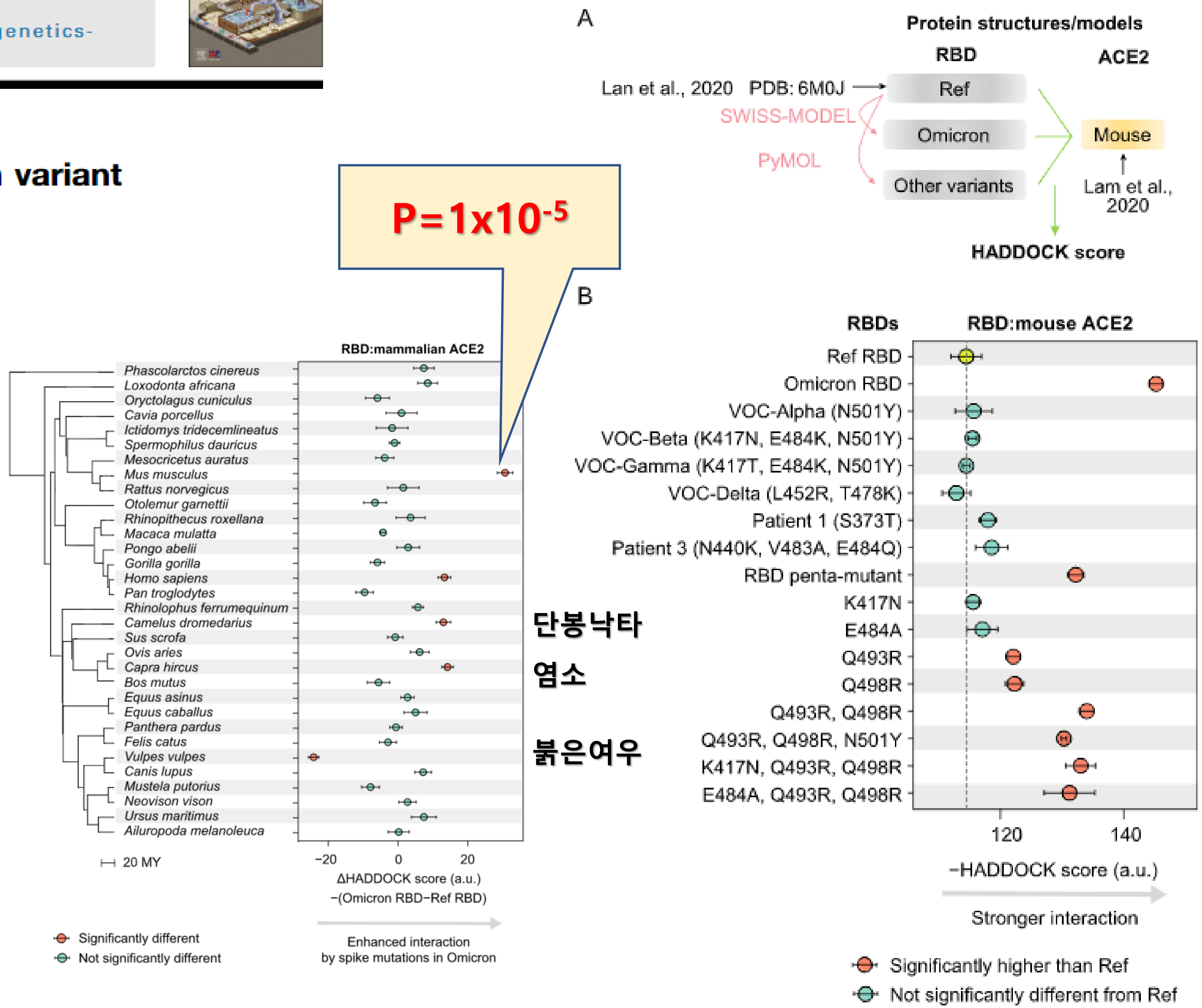
Original research

Evidence for a mouse origin of the SARS-CoV-2 Omicron variant

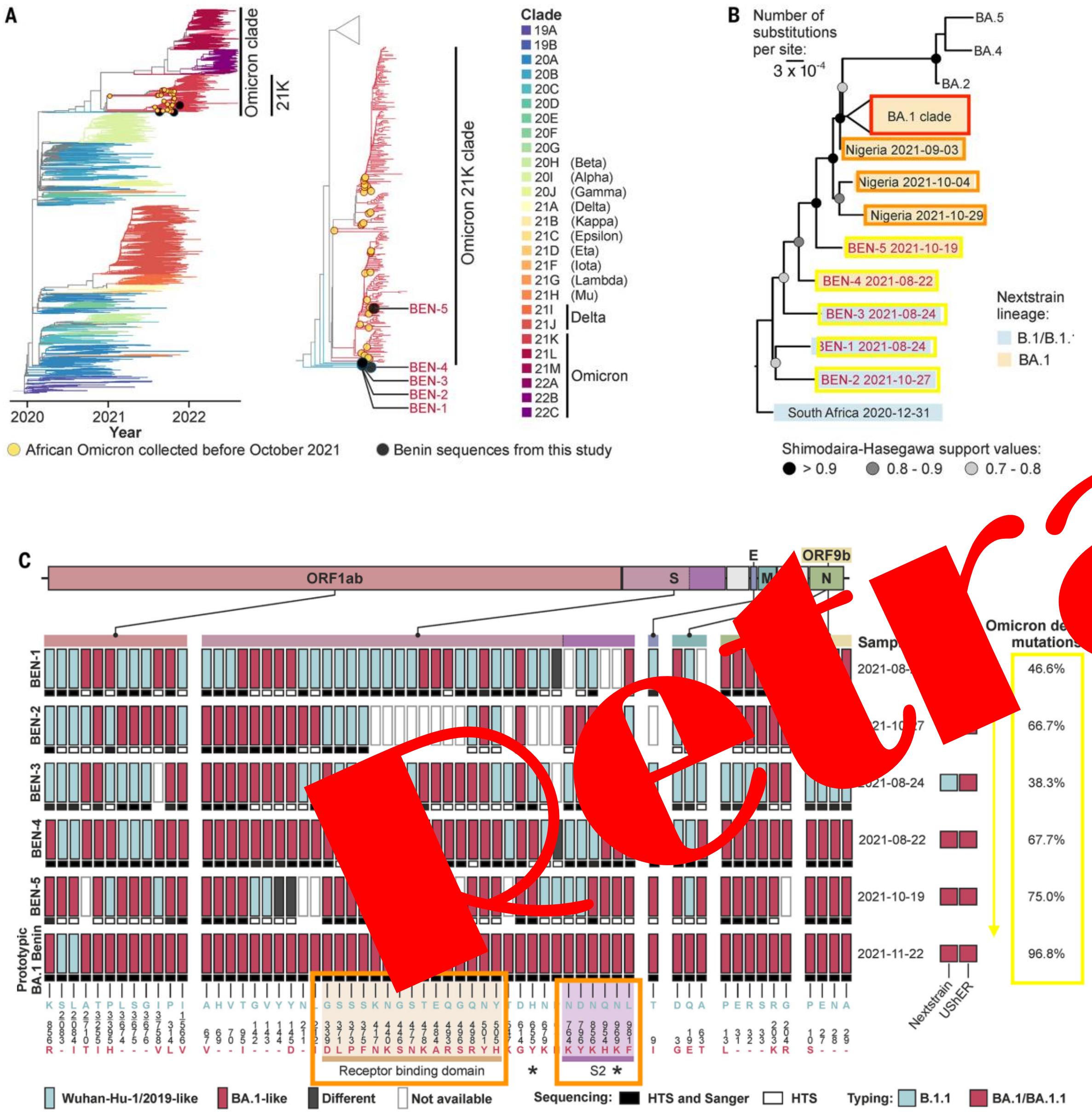
2021 Dec;48(12):1111-1121.

B **Step 4: Performing principal component analysis for molecular spectra**





Gradual Evolution of BA.1 originating from West Africa



Science RESEARCH ARTICLES

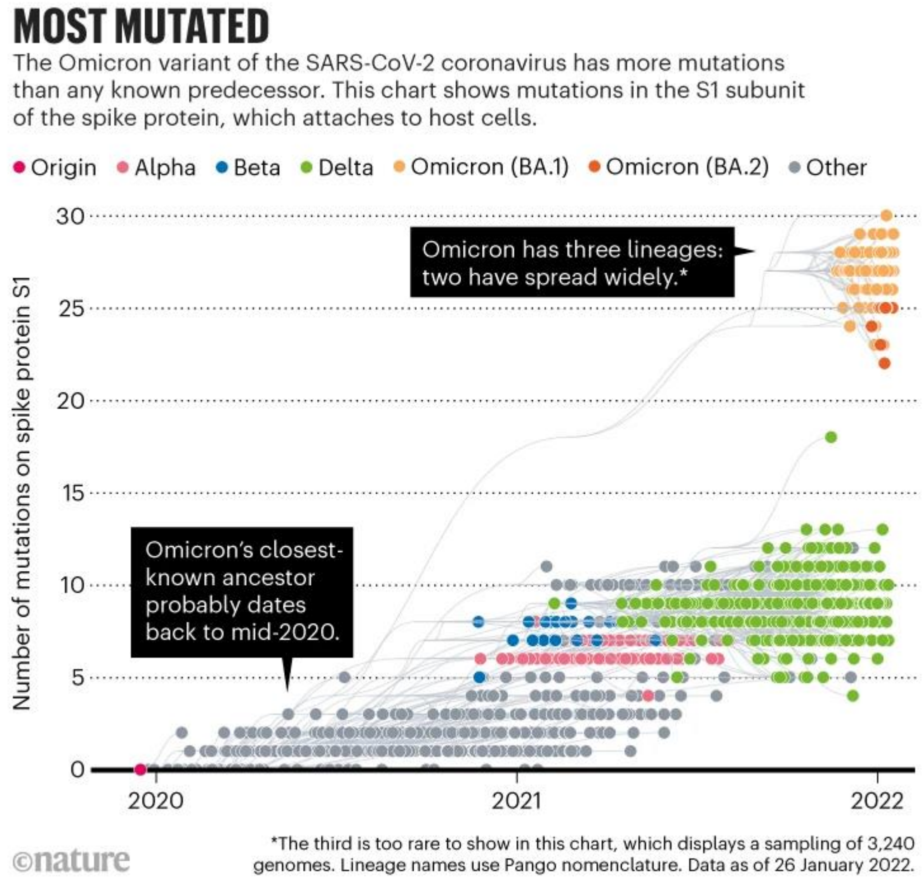
Cite as: C. Fischer *et al.*, *Science* 10.1126/science.add8737 (2022).

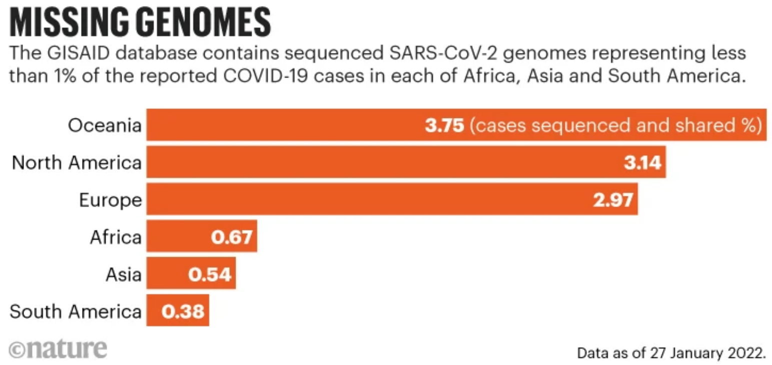
Gradual emergence followed by exponential spread of the SARS-CoV-2 Omicron variant in Africa

- BA.1 would not abruptly emerge from South Africa
- Heterogeneous sampling intensity by countries in Africa might lead to sampling bias in the previous study

Less likely – Non-Human host & Immunocompromised individual

Mysterious Origin of the Omicron





The mysterious origins of the Omicron variant of SARS-CoV-2

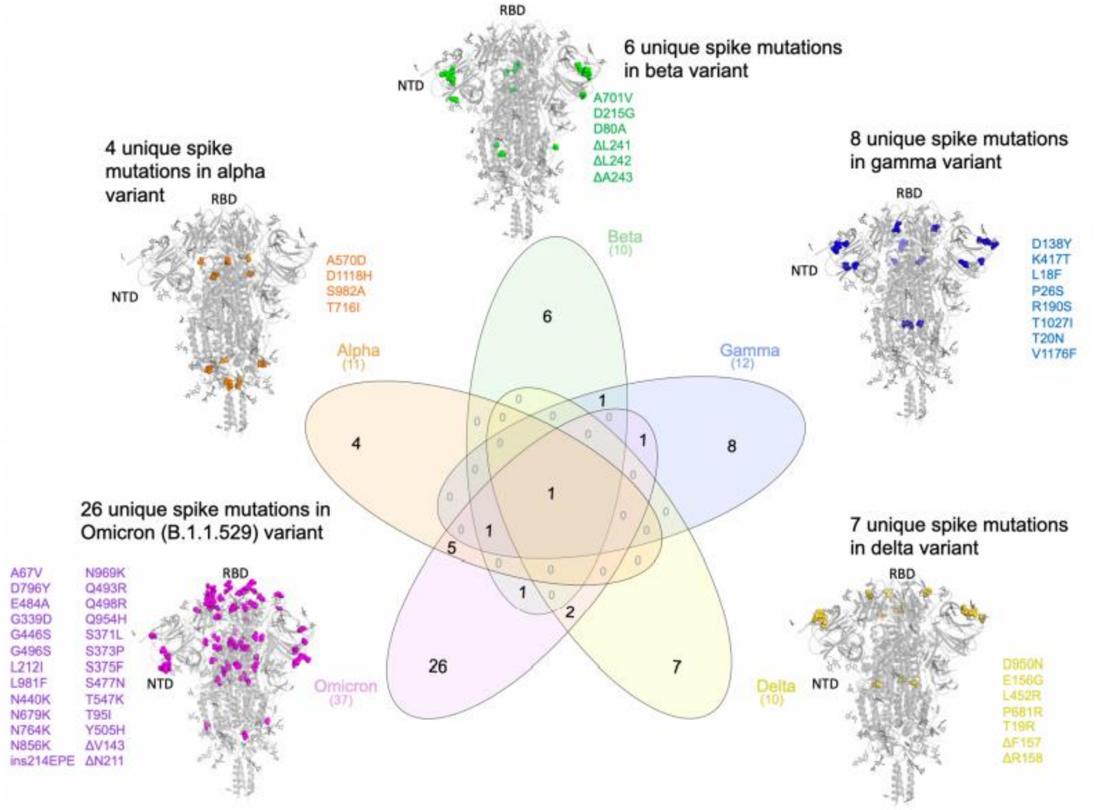
Pei Du,[1] George Fu Gao,[1,2,3] and Qihui Wang[1,2,*]
[1]CAS Key Laboratory of Pathogen Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences (CAS), Beijing 100101, China
[2]University of Chinese Academy of Sciences, Beijing 100049, China
[3]Chinese Center for Disease Control and Prevention (China CDC), Beijing 102206, China

Innovation (Camb). 2022 Mar29 ; 3(2):100206

1) Omicron could have circulated and evolved in a **hidden population**
2) Omicron may have evolved from a cat-and-mouse game between the virus and host in some **immunosuppressed patients**; for example, AIDS patients infected with SARS-CoV-2
3) Omicron could have originated from adaptation in **animal reservoirs** and been transmitted back to human, exemplified by the SARS-CoV-2 variants with mutations from adapting to mink
4) It appears **all three theories may contribute to the generation of Omicron**, making the origins of Omicron a complicated question involving three different origins

SARS-CoV-2 Omicron variant; Spike mutation summary

고려대학교 의과대학
Korea University College of Medicine

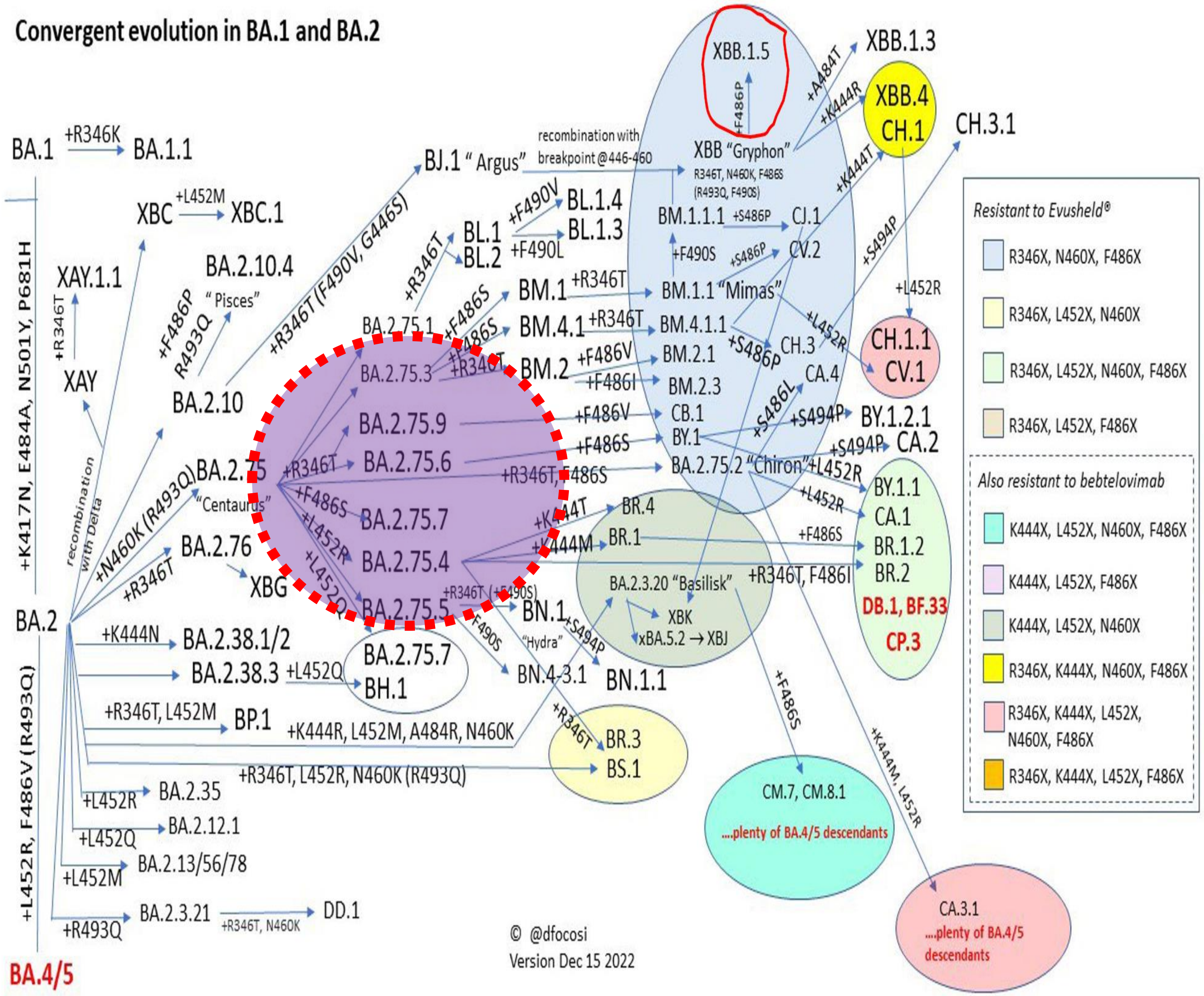


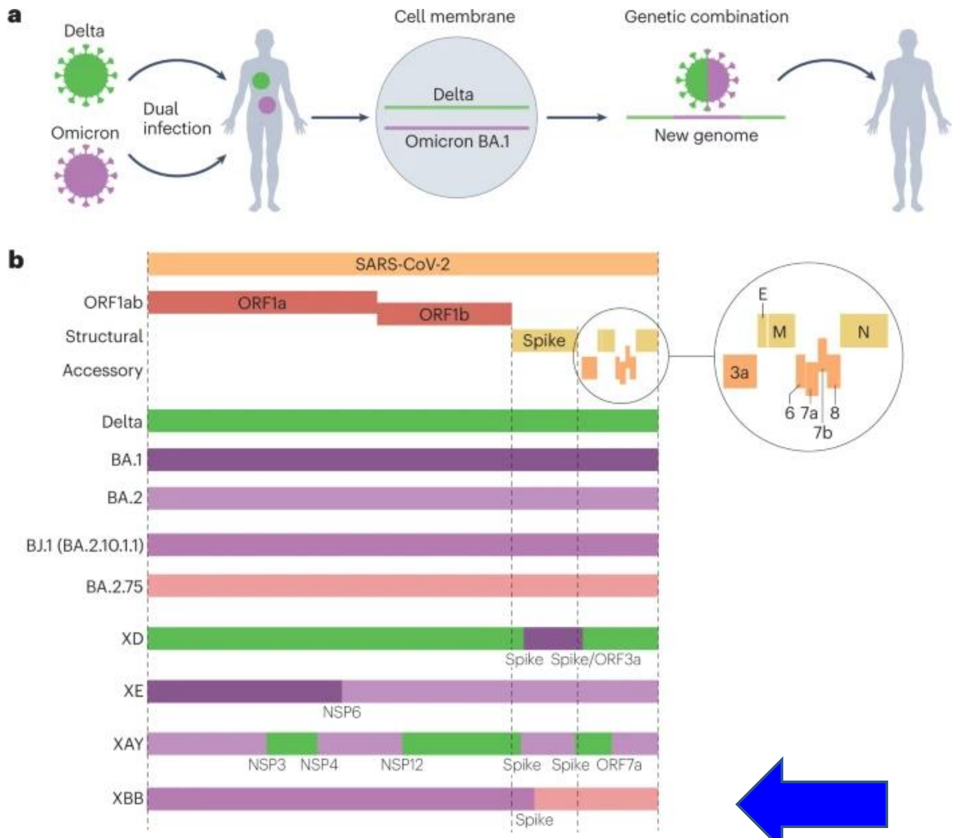

```
>P0DTC2      MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFS    60
>B.1.1.529   MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFS    60

>P0DTC2      NVTWFHAIHVSGTNGTKRFDNPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIV   120
>B.1.1.529   NVTWFHVI--SGTNGTKRFDNPVLPFNDGVYFASIEKSNIIRGWIFGTTLDSKTQSLLIV   118

>P0DTC2      NNATNVVIKVCEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLE   180
>B.1.1.529   NNATNVVIKVCEFQFCNDPFLD---HKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLE   175
                                       ins214EPE:
>P0DTC2      GKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVR---DLPQGFSALEPLVDLPIGINITRFQT   240
>B.1.1.529   GKQGNFKNLREFVFKNIDGYFKIYSKHTPI-IVREPEDLPQGFSALEPLVDLPIGINITRFQT   237

>P0DTC2      LLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETK   300
>B.1.1.529   LLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETK   297
```

20I (Alpha, V1) (B.1.1.7)	20H (Beta, V2) (B.1.351)	20J (Gamma, V3) (P.1)	21A (Delta) (B.1.617.2)	21B (Kappa) (B.1.617.1)	21K (Omicron) (B.1.1.529)	21D (Eta) (B.1.525)	21F (Iota) (B.1.526)	21G (Lambda) (C.37)	21H (Mu) (B.1.621)	20A/S:126A (B.1.620)
					Shared mutations					
	Sort by:				Commonness Position					
	S: L 18 F	S: L 18 F								
		S: P 26 S								S: P 26 S
					S: A 67 V	S: A 67 V				
S: H 69 -					S: H 69 -	S: H 69 -				S: H 69 -
S: V 70 -					S: V 70 -	S: V 70 -				S: V 70 -
					S: T 95 I		S: T 95 I		S: T 95 I	
S: Y 144 -					S: Y 144 -	S: Y 144 -			S: Y 144 S	S: Y 144 -
					S: Y 145 D				S: Y 145 N	
	S: L 241 -									S: L 241 -
	S: L 242 -									S: L 242 -
	S: A 243 -									S: A 243 -
							S: D 253 G	S: D 253 N		
	S: K 417 N	S: K 417 T			S: K 417 N					
			S: L 452 R	S: L 452 R				S: L 452 Q		
					S: S 477 N					S: S 477 N
			S: T 478 K		S: T 478 K					
	S: E 484 K	S: E 484 K		S: E 484 Q	S: E 484 A	S: E 484 K	S: E 484 K		S: E 484 K	S: E 484 K
S: N 501 Y	S: N 501 Y	S: N 501 Y			S: N 501 Y				S: N 501 Y	
S: D 614 G	S: D 614 G	S: D 614 G	S: D 614 G	S: D 614 G	S: D 614 G	S: D 614 G	S: D 614 G	S: D 614 G	S: D 614 G	S: D 614 G
		S: H 655 Y			S: H 655 Y					
S: P 681 H			S: P 681 R	S: P 681 R	S: P 681 H				S: P 681 H	S: P 681 H
	S: A 701 V						S: A 701 V			
			S: D 950 N						S: D 950 N	
		S: T 1027 I								S: T 1027 I
S: D 1118 H										S: D 1118 H
					Other mutations					
S: A 570 D	S: D 80 A	S: T 20 N	S: T 19 R	S: E 154 K	S: G 142 -	S: Q 52 R	S: L 5 F	S: G 75 V	S: R 346 K	S: V 126 A
S: T 716 I	S: D 215 G	S: D 138 Y	S: E 156 -	S: Q 1071 H	S: V 143 -	S: Q 677 H		S: T 76 I		S: H 245 Y
S: S 982 A		S: R 190 S	S: F 157 -		S: N 211 -	S: F 888 L		S: R 246 -		
		S: V 1176 F	S: R 158 G		S: G 339 D			S: S 247 -		
					S: S 371 L			S: Y 248 -		
					S: S 373 P			S: L 249 -		
					S: S 375 F			S: T 250 -		
					S: N 440 K			S: P 251 -		
					S: G 446 S			S: G 252 -		
					S: Q 493 R			S: F 490 S		
					S: G 496 S			S: T 859 N		
					S: Q 498 R					
					S: Y 505 H					
					S: T 547 K					
					S: N 679 K					
					S: N 764 K					
					S: D 796 Y					
					S: N 856 K					
					S: Q 954 H					
					S: N 969 K					

Venkata Krishnan, et al., (2021, December 3). https://doi.org/10.31219/osf.io/f7txy (Pre-prin

Convergent Evolution in BA.1 and BA.2





❖ **Due to high levels of co-circulation between Delta and BA.1, or BA.1 and BA.2, in many countries at a time of phasing out of COVID-19 restrictions, 2022**

Carabelli, A.M., *et al.* SARS-CoV-2 variant biology: immune escape, transmission and fitness. *Nat Rev Microbiol* 21, 162–177 (2023).

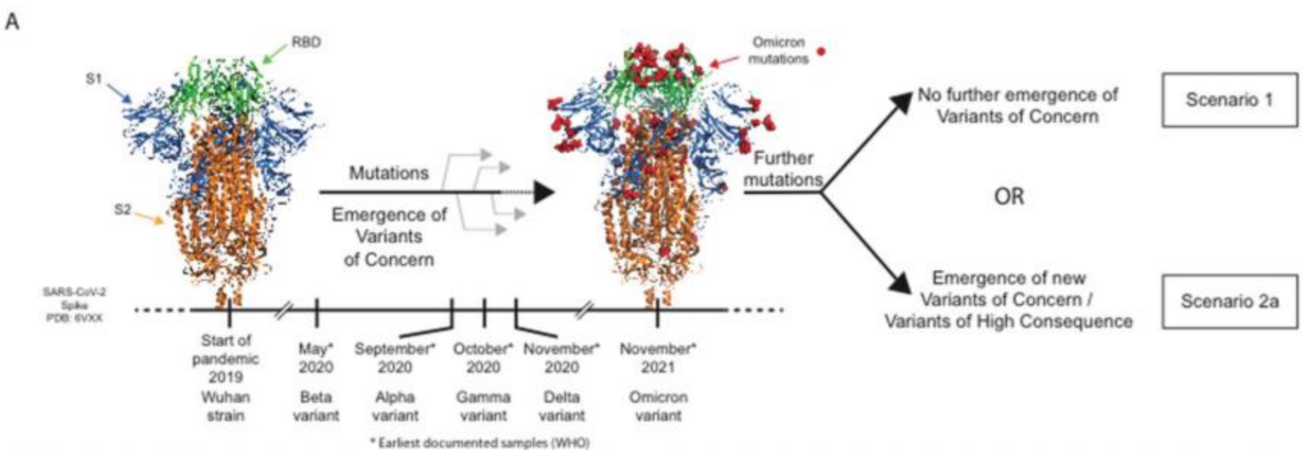
viruses
MDPI

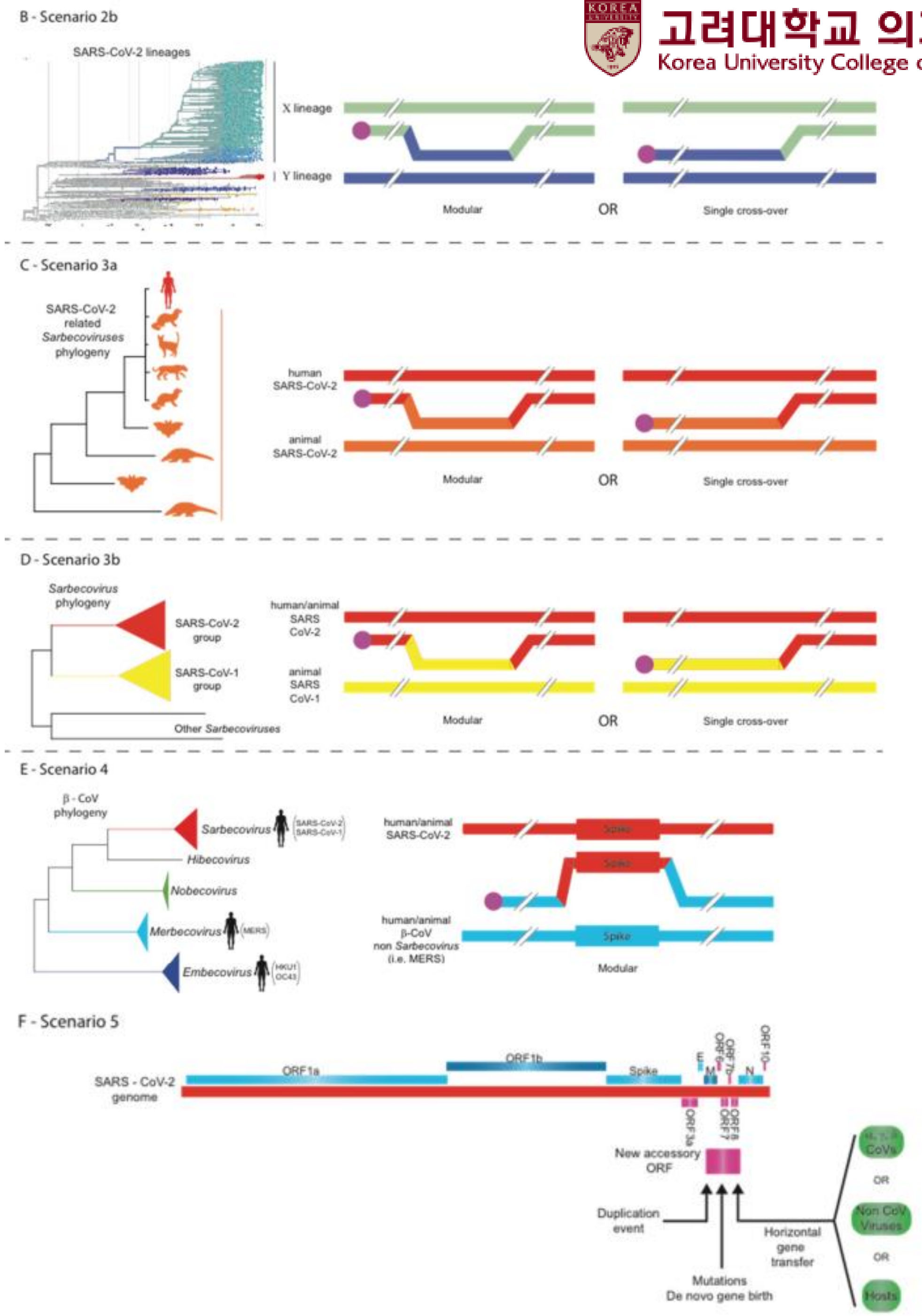
Review

The Remarkable Evolutionary Plasticity of Coronaviruses by Mutation and Recombination: Insights for the COVID-19 Pandemic and the Future Evolutionary Paths of SARS-CoV-2

Grigorios D. Amoutzias [1,*], Marios Nikolaidis [1], Eleni Tryfonopoulou [2], Katerina Chlichlia [2], Panayotis Markoulatos [3] and Stephen G. Oliver [4,*]

고려대학교 의과대학
Korea University College of Medicine





(A) Scenario 1: structural constraints limit any further evolution of the SARS-CoV-2 spike

(B) Scenario 2a: point mutations, insertions/deletions, and/or intra-SARS-CoV-2 recombination events lead to the evolution of novel SARS-CoV-2 strains.

(C) Scenario 2b: intra-SARS-CoV-2 recombination events lead to the evolution of novel SARS-CoV-2 strains.

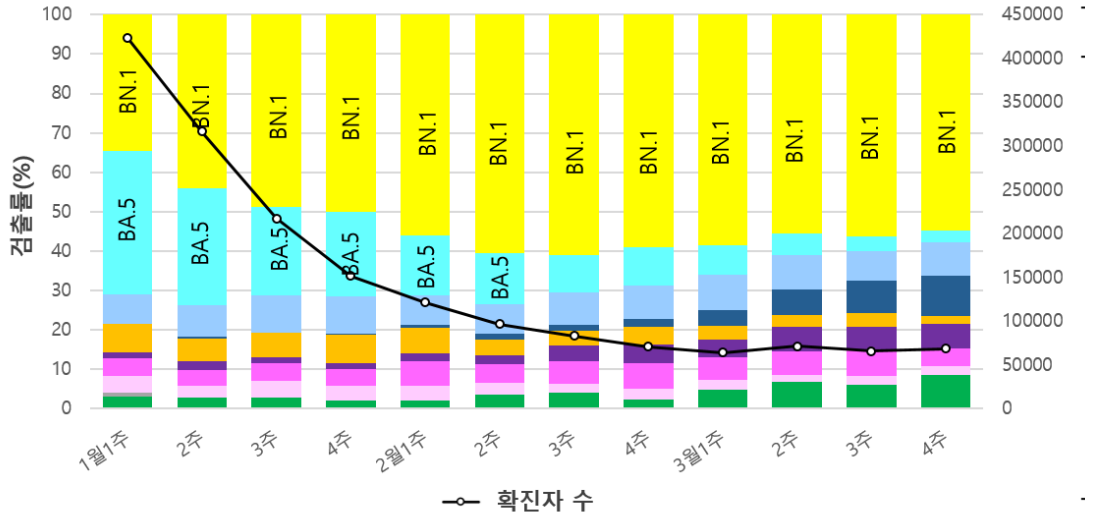
(D) Scenario 3a: intratypic recombinations between SARS-CoV-2 and closely related sarbecoviruses.

(E) Scenario 3b: intratypic recombinations between SARS-CoV-2 and other related sarbecoviruses.

(F) Scenario 4: intertypic recombination between SARS-CoV-2 and viruses from other Beta-CoV subgenera.

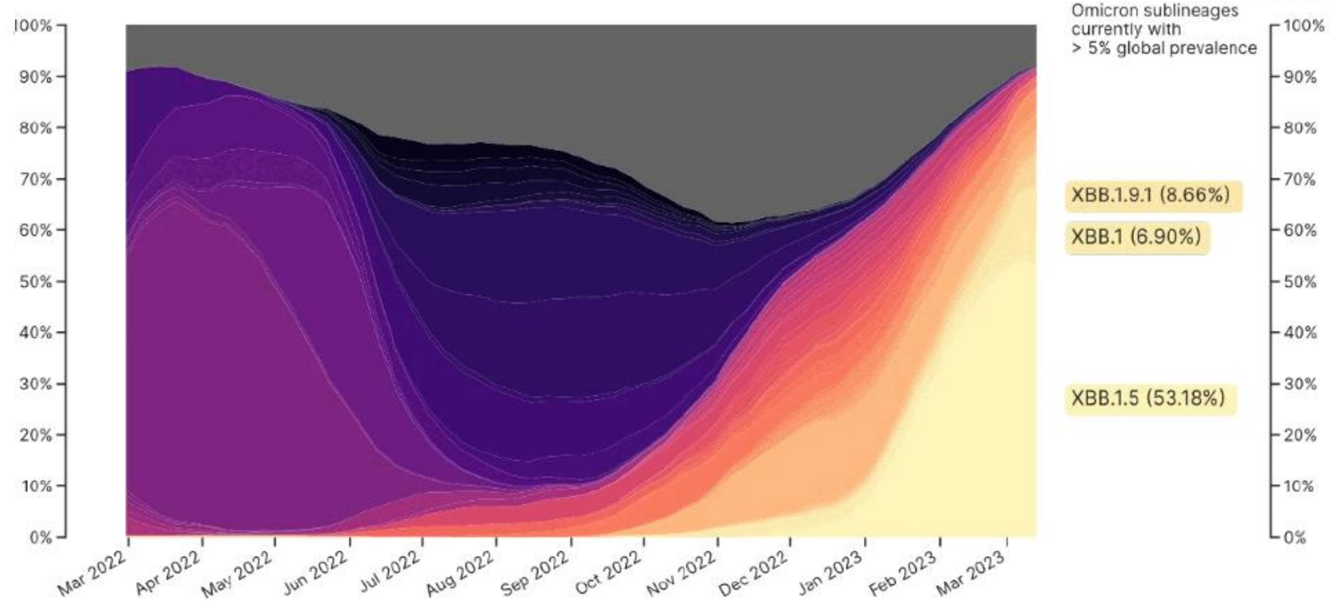
(G) Scenario 5: non-homologous recombination of SARS-CoV-2 with other coronaviruses or even other viruses/hosts

Current Situation of SARS-CoV-2 variants

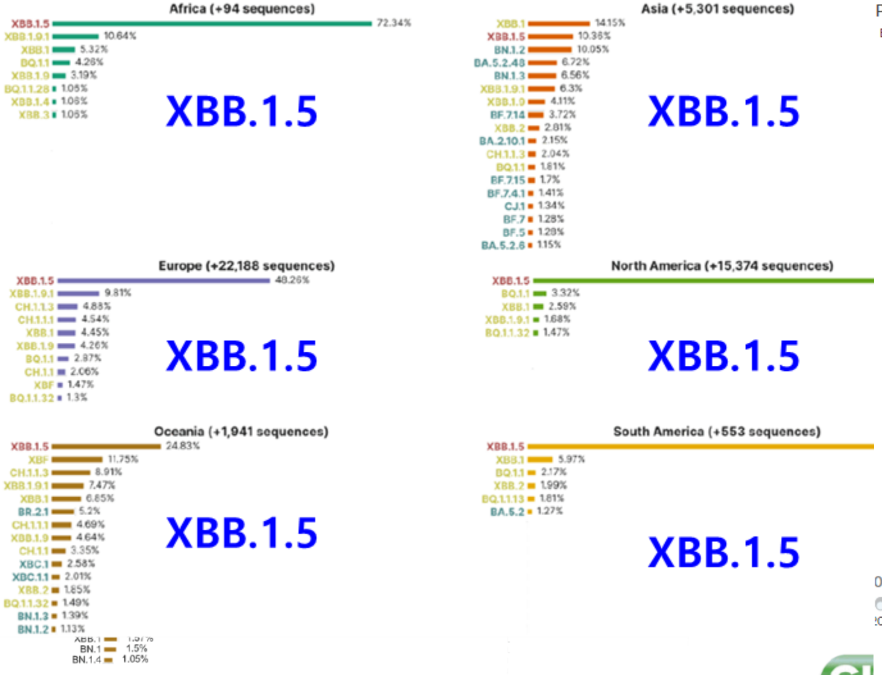


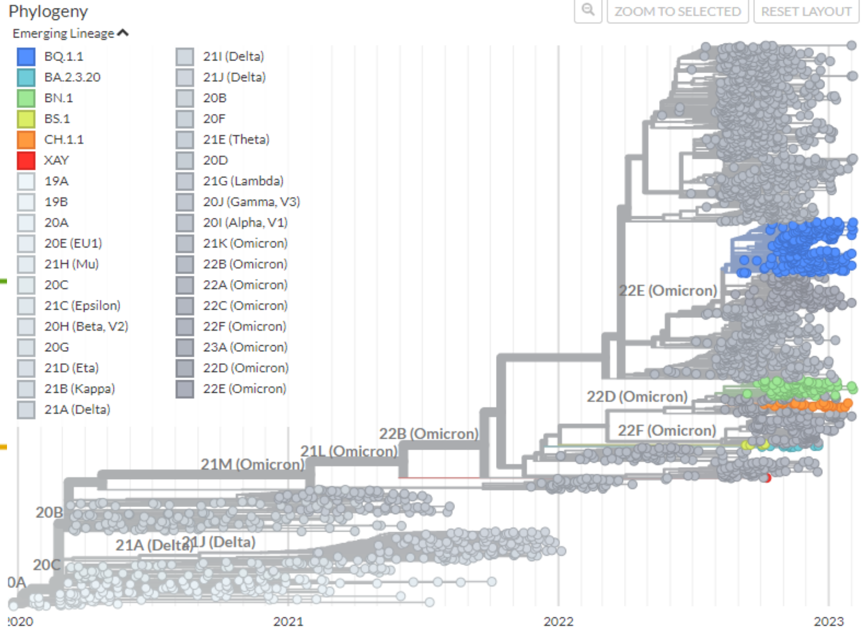
Timecourse of Omicron variant sublineage distribution

2023-03-28



WHO	세부계통	점유율(%)	비고
오미크론	BN.1	54.8	
	XBB.1.5	10.1	
	BQ.1	8.6	
	CJ.1	6.2	
	CH.1.1	4.6	
	BA.5	2.9	
	BQ.1.1	2.2	
	BA.2.75	2.0	
	기타	8.6	



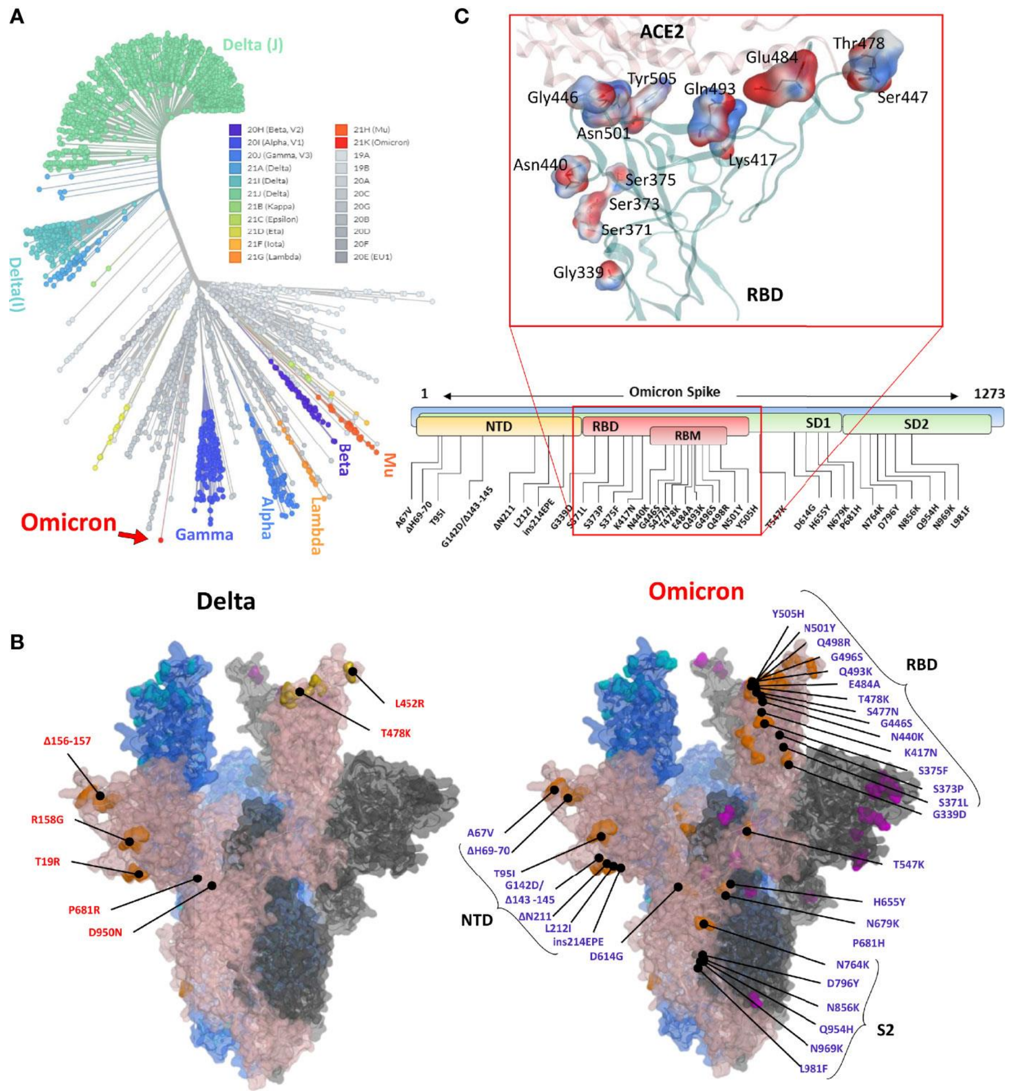


질병관리청 (23.3.22)

GISAID / Nextstrain

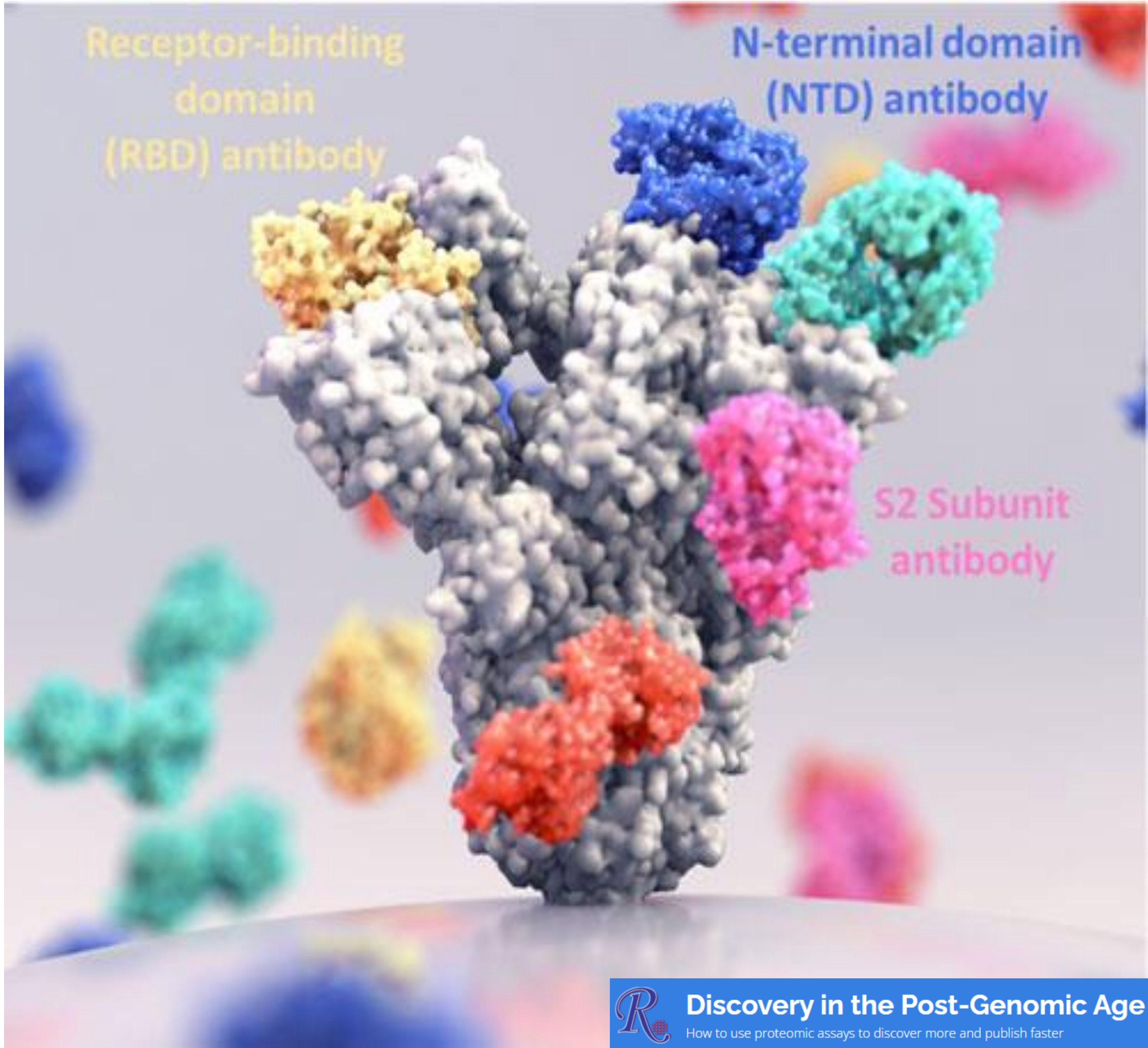
SARS-CoV-2 antibody binding properties

고려대학교 의과대학
Korea University College of Medicine

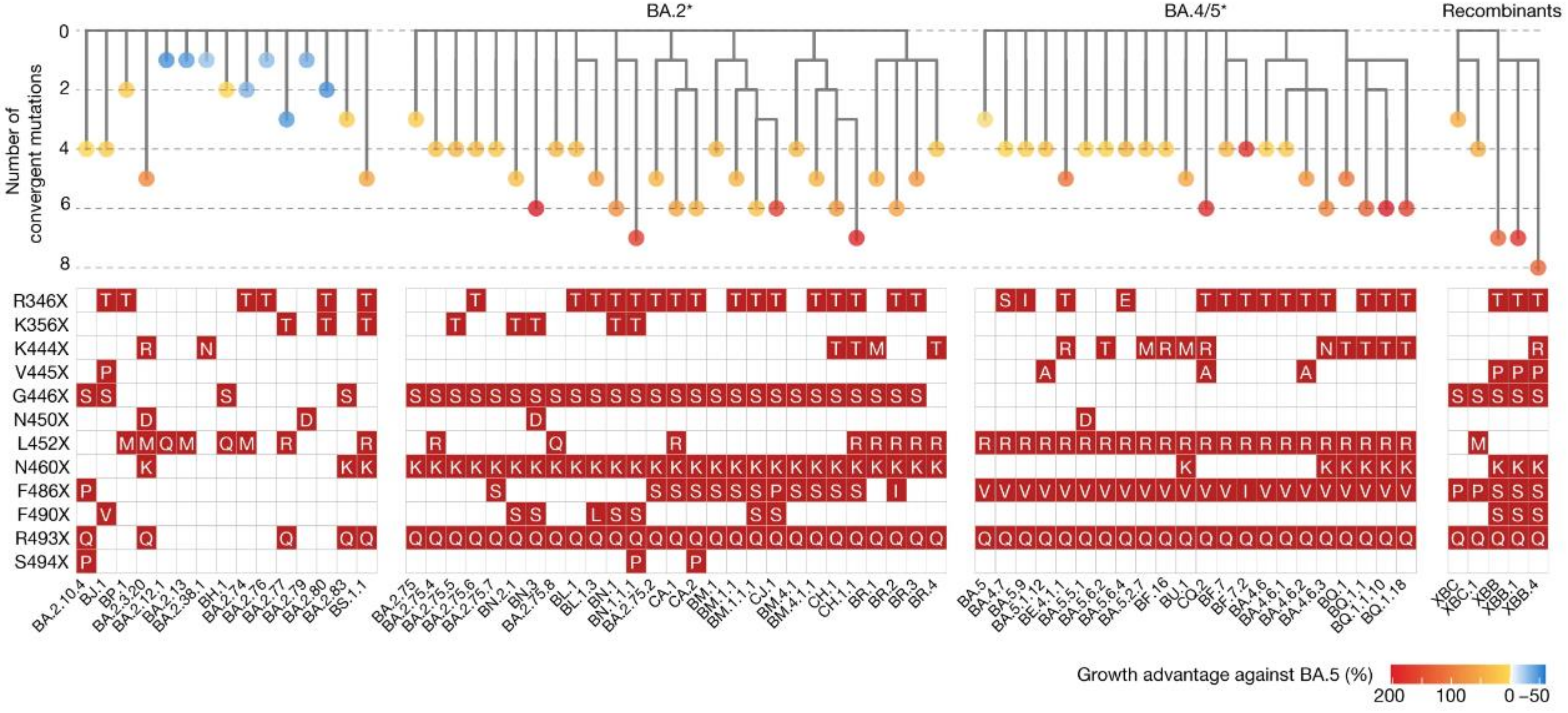


Receptor Binding and Immune Escape of the Omicron

Front. Immunol. 12:830527, 2021



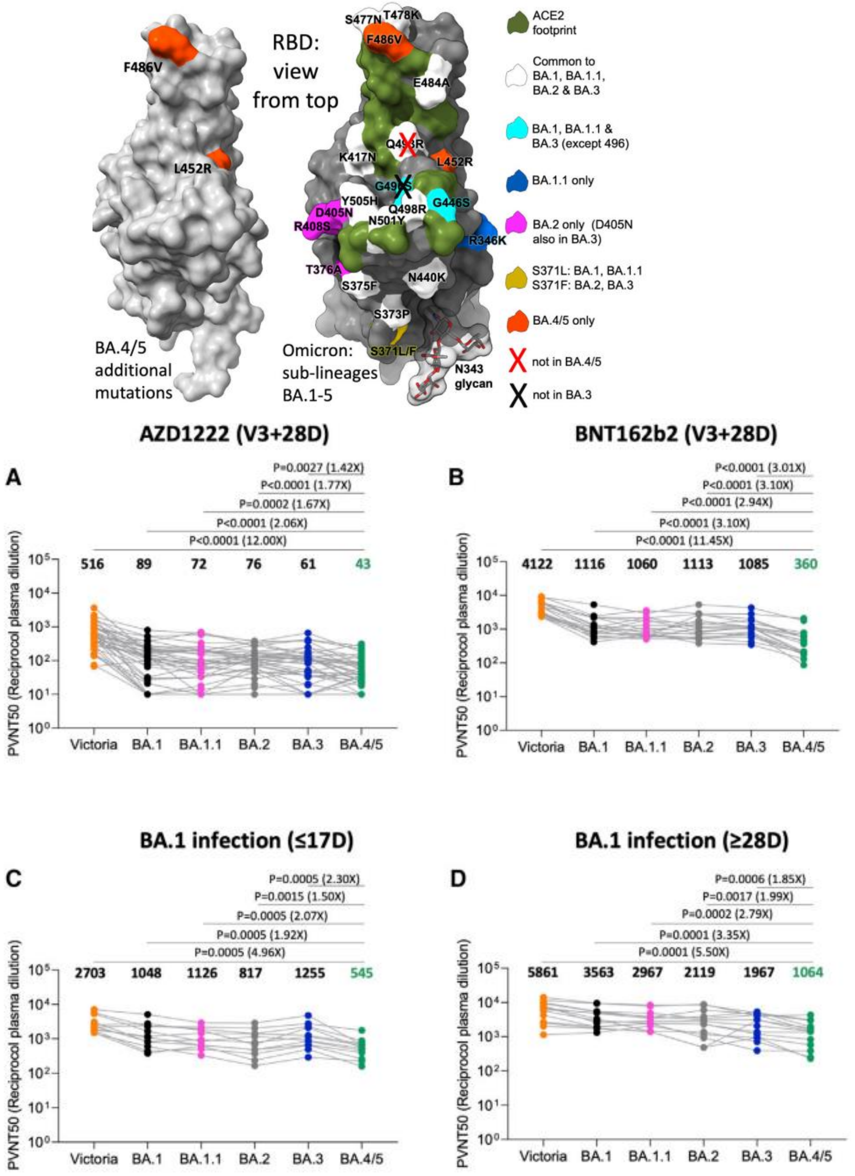
Alteration of Omicron RBD with growth advantage over BA.5.



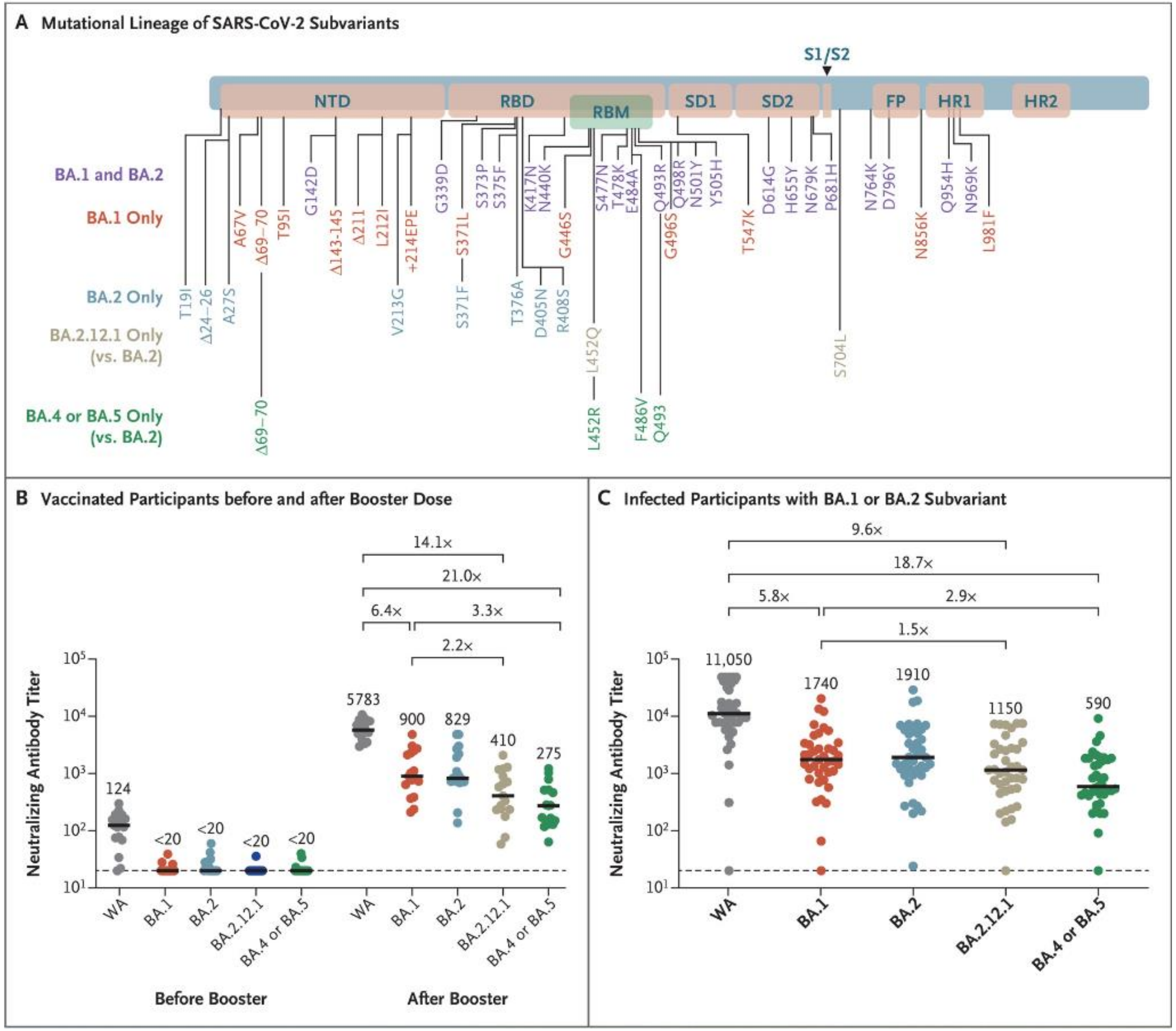
Cao, Y., Jian, F., Wang, J. *et al.* Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution. *Nature* (2022). https://doi.org/10.1038/s41586-022-05644-7

Reduced neutralizing effect against omicron sub-variants

고려대학교 의과대학
Korea University College of Medicine



Pseudoviral neutralization assays of
BA.4/5 by vaccine and BA.1 immune serum



Cell 185, 2422–2433, 2022

N Engl J Med 2022; 387:86-88

고려대학교 의과대학
Korea University College of Medicine

Reduced IC_{50} of therapeutic NAbs against emerging SARS-CoV-2 BA.2, BA.5 or BA.2.75 convergent subvariants

a

Pango lineages	REGN 10933	REGN 10987	REGN10933 + 10987	COV2 -2196	COV2 -2130	COV2-2196 + 2130	BRII-196	BRII-198	BRII-196 + 198	S309	DXP-604	LY-CoV 1404	SA58	SA55	SA55 + SA58	Additional RBD mutations
BA.2	*	590	821	4,312	6.3	8.2	8,530	8,990	8,610	852	219	0.9	5.1	7.2	7.8	
BA.2.3.20	111	*	201	12	*	23	4,591	*	8,823	961	6,990	7.9	18	3.9	7.5	K444R + N450D + L452M + N460K + A484R + R493Q
BS.1.1	92	435	177	790	*	1,100	2,011	*	4,012	*	7,803	1.3	5,981	5.1	9.9	R346T + K356T + L452R + N460K + G476S + R493Q
XBC	*	*	*	*	12	21	*	*	*	69	*	0.8	20	5.2	7.0	D339G + G446S + F486P + R493Q
XBB	*	*	*	*	*	*	*	*	*	963	*	*	8,805	5.3	9.8	D339H + R346T + L368I + V445P + G446S + N460K + F486S + F490S + R493Q
BA.2.75	278	*	410	119	352	121	1,730	6,622	3,861	672	5,920	2.2	246	4.3	9.6	
BN.1	344	*	599	70	*	166	3,683	*	7,791	*	6,012	3.3	8,295	4.9	9.0	R346T + K356T + F490S
BA.2.75.2	*	*	*	*	*	*	*	*	*	852	*	3.0	6,922	5.9	9.7	R346T + F486S
BM.1.1.1	*	*	*	*	*	*	*	*	*	956	*	1.9	8,082	4.8	10	R346T + F486S + F490S
CJ.1	*	*	*	*	*	*	*	*	*	747	*	5.0	8,024	5.1	9.8	R346T + F486P + F490S
BR.2	*	*	*	*	*	*	*	*	*	921	*	2.6	7,263	4.7	11	R346T + L452R + F486I
CA.1	*	*	*	*	*	*	*	*	*	897	*	3.2	6,927	6.0	12	R346T + L452R + F486S
CA.2	*	*	*	*	*	*	*	*	*	683	*	1.7	6,789	4.9	9.7	R346T + F486S + S494P
CH.1.1	*	*	*	*	*	*	*	*	*	924	*	*	*	7.1	11	R346T + K444T + L452R + F486S
BA.4/5	*	520	709	*	23	40	7,124	*	*	1,055	6,264	0.8	3.9	5.0	4.5	
BF.7	*	2,195	4,388	*	*	*	4,356	*	8,307	3,543	4,116	1.0	341	6.6	9.0	R346T
BA.5.6.2	*	*	*	*	*	*	4,636	*	7,883	1,408	5,892	1,662	58	5.1	8.9	K444T
BU.1	*	*	*	*	*	*	*	*	*	1,082	*	26	56	5.3	11	K444M + N460K
BQ.1	*	*	*	*	*	*	*	*	*	1,709	*	1,905	44	6.6	9.2	K444T + N460K
BQ.1.1	*	*	*	*	*	*	*	*	*	5,581	*	*	900	5.9	10	R346T + K444T + N460K
BA.4.6.3	*	*	*	*	*	*	*	*	*	4,987	*	*	1,809	6.7	9.9	R346T + K444N + N460K

Pseudovirus IC_{50} ($\mu g\ ml^{-1}$) | <100 | 100–1,000 | >1,000 | *>10,000

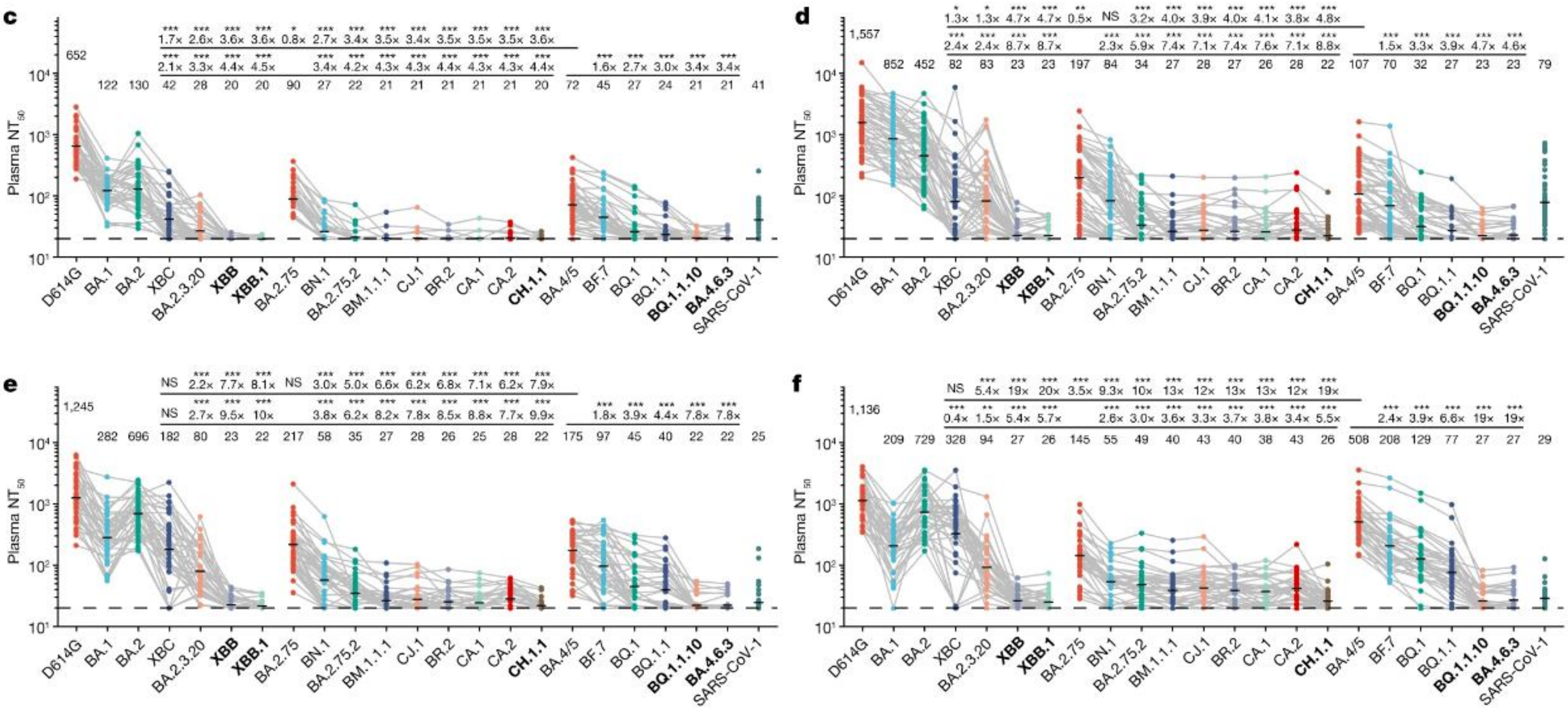
Cao, Y., et al. Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution. Nature 614, 521–529 (2023).

Omicron subvariants induce NAb evasion

Cao, Y., et al. Nature 614, 521–529 (2023).

three doses of CoronaVac (n = 40)

infected with BA.1 after three doses of CoronaVac (n = 50)

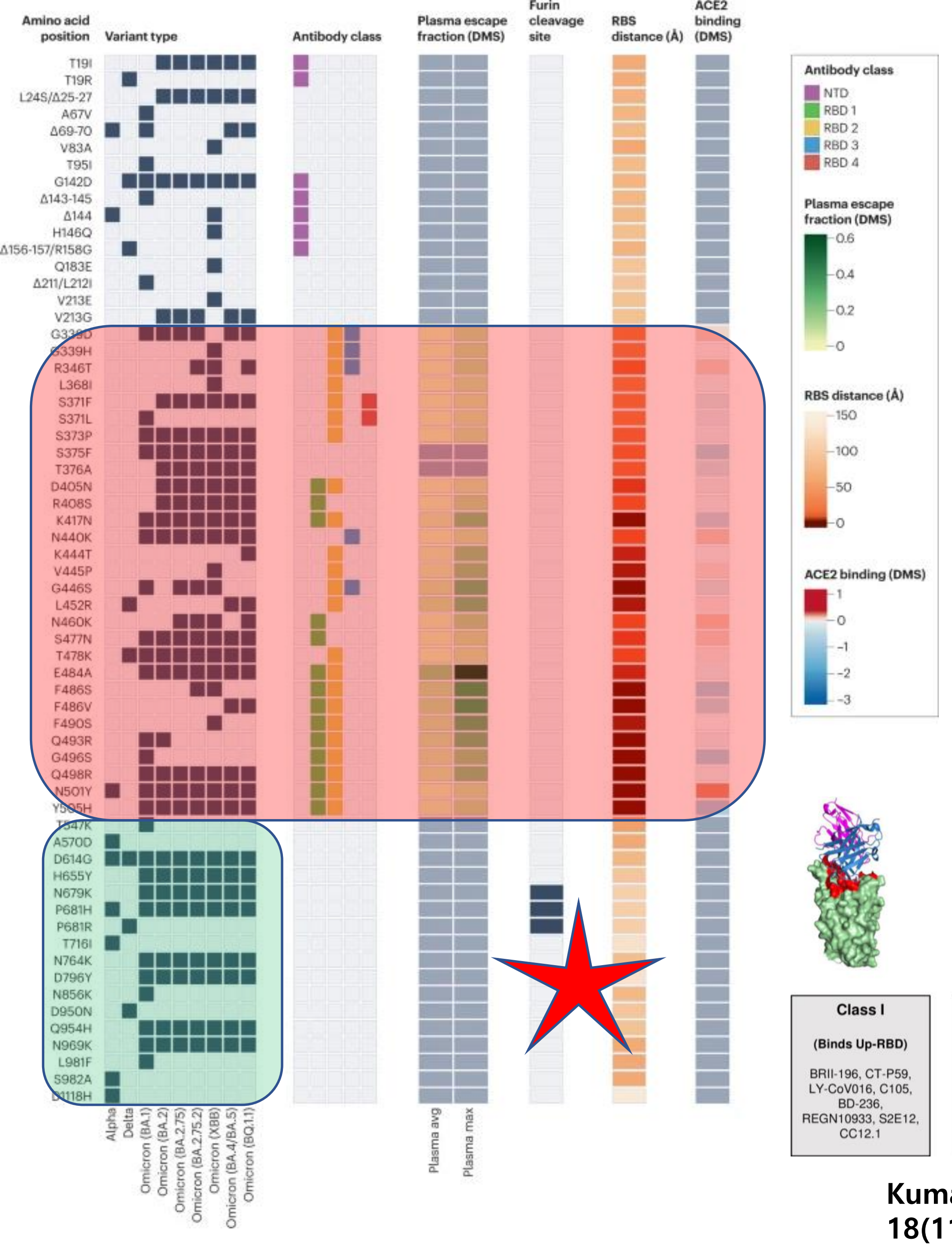


infected with BA.2 after three doses of CoronaVac (n = 39)

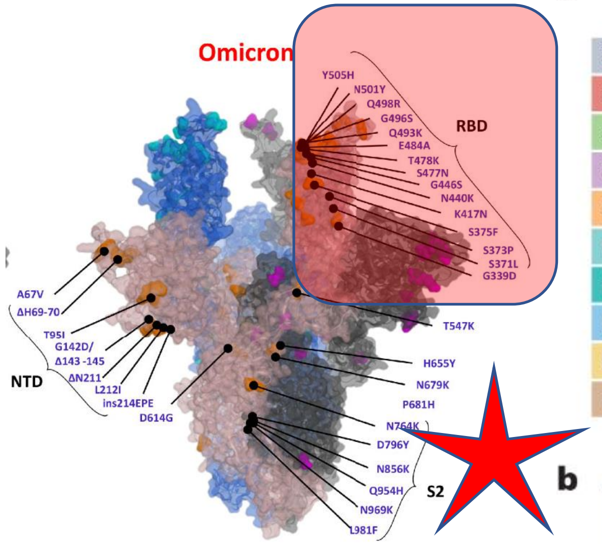
infected with BA.5 after three doses of CoronaVac (n = 36)

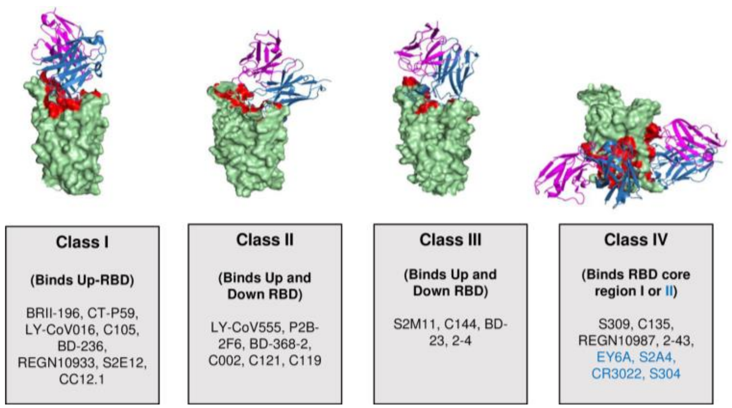
고려대학교 의과대학
Korea University College of Medicine

Properties of amino acid substitutions or deletions in selected SARS-CoV-2 variants

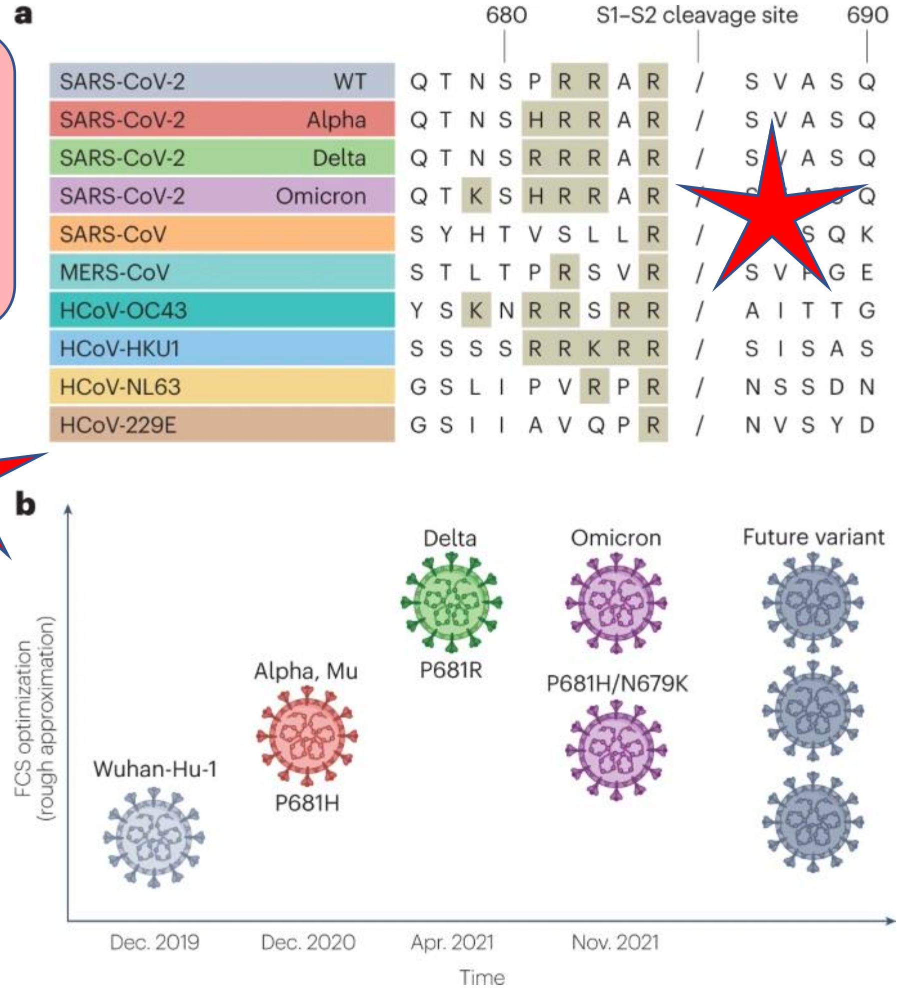


Carabelli, A.M., *et al. Nat Rev Microbiol* 21, 162–177 (2023).





Kumar S, et al., PLOS Pathogens 18(11): e1010983, 2022

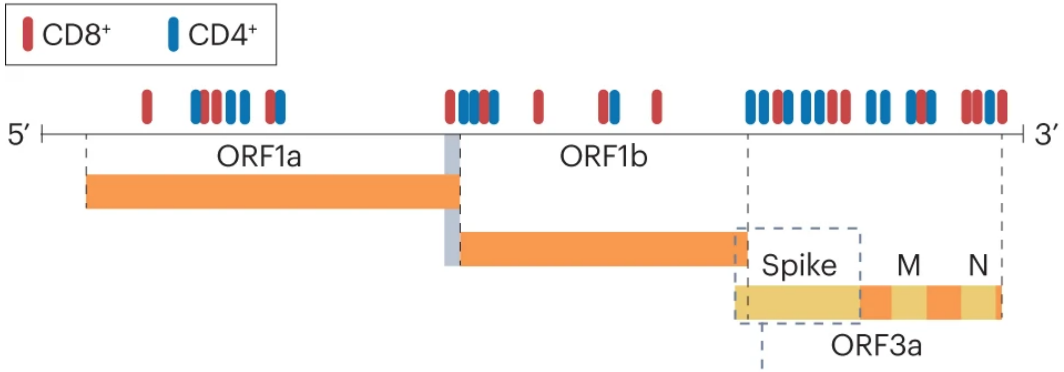


Furin cleavage site
➔ trafficking of the virus to the cell surface

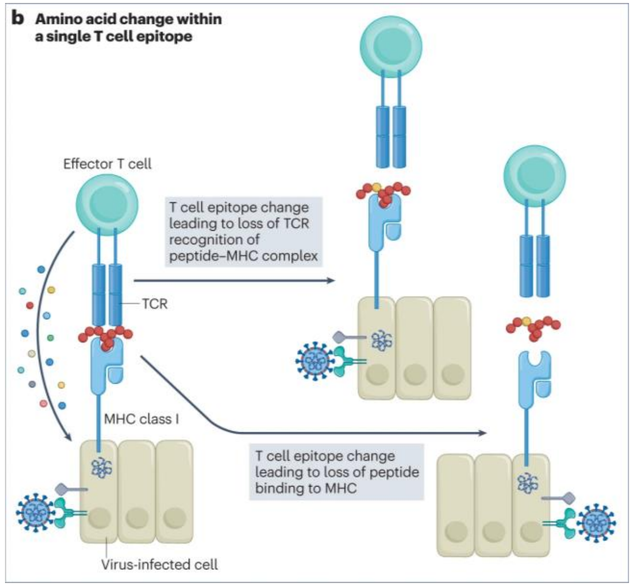
Reduced T cell mediated immunity against omicron sub-variants

고려대학교 의과대학
Korea University College of Medicine

a Breadth of T cell epitopes targeted in an individual after SARS-CoV-2 infection



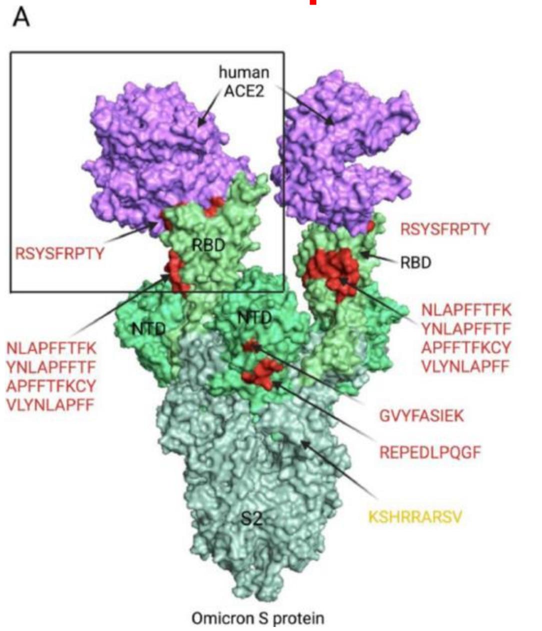
After infection, CD4+ T cell and CD8+ T cell responses are generated against 30–40 epitopes across the virus genome



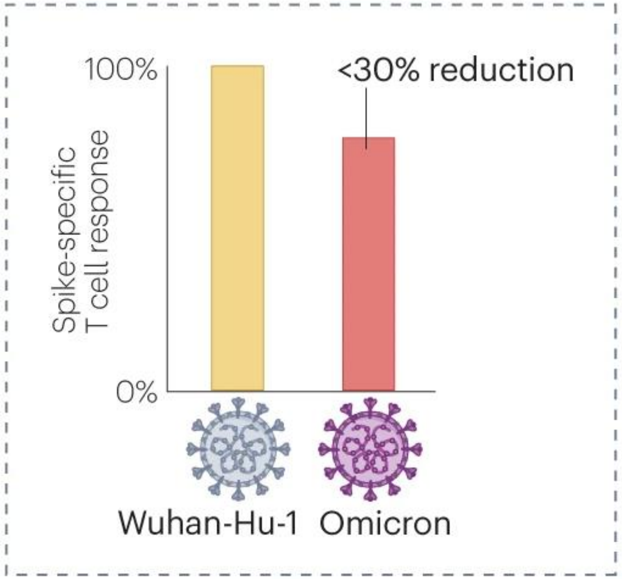
Carabelli, A.M., *et al. Nat Rev Microbiol* 21, 162–177 (2023).

❖T cell response to vaccination is focused on the spike protein alone

- Most high-frequency spike CD4+ epitope responses are focused on discrete regions of the NTD
- Mutations concentrated in the spike RBD and NTD found in many VOCs might be driven by antibody evasion
- Therefore mutation resulted form vaccine escape have limited impact on the overall T cell response



Simone P. et al., ImmunoInformatics, 2022



c Impact of Omicron mutations on T cell response following vaccination

Vaccine Effectiveness against Major variants

고려대학교 의과대학
Korea University College of Medicine

	Effectiveness at preventing													
	Ancestral		Alpha		Beta		Gamma		Delta		BA.1/BA.2		BA.5	
Vaccine	Severe disease	Infection	Severe disease	Infection	Severe disease	Infection	Severe disease	Infection	Severe disease	Infection	Severe disease	Infection	Severe disease	Infection
AstraZeneca	94%	63%	94%	63%	94%	69%	94%	69%	94%	69%	71%	36%	71%	36%
CanSino	66%	62%	66%	62%	64%	61%	64%	61%	64%	61%	48%	32%	48%	32%
CoronaVac	50%	47%	50%	47%	49%	46%	49%	46%	49%	46%	37%	24%	37%	24%
Covaxin	78%	73%	78%	73%	76%	72%	76%	72%	76%	72%	57%	38%	57%	38%
Johnson & Johnson	86%	72%	86%	72%	75%	64%	76%	64%	76%	64%	57%	33%	57%	33%
Moderna	97%	92%	97%	92%	97%	91%	97%	91%	97%	91%	[illegible]	48%	73%	48%
Novavax	89%	83%	89%	83%	85%	82%	86%	82%	86%	82%	65%	43%	65%	43%
Pfizer/BioNTech	95%	86%	95%	86%	95%	84%	95%	84%	95%	84%	72%	44%	72%	44%
Sinopharm	73%	68%	73%	68%	71%	67%	71%	67%	71%	67%	53%	35%	53%	35%
Sputnik-V	92%	86%	92%	86%	89%	85%	89%	85%	89%	85%	67%	44%	67%	44%
Other vaccines	75%	70%	75%	70%	73%	69%	73%	69%	73%	69%	55%	36%	55%	36%
Other vaccines (mRNA)	91%	86%	91%	86%	88%	85%	88%	85%	88%	85%	67%	45%	67%	45%

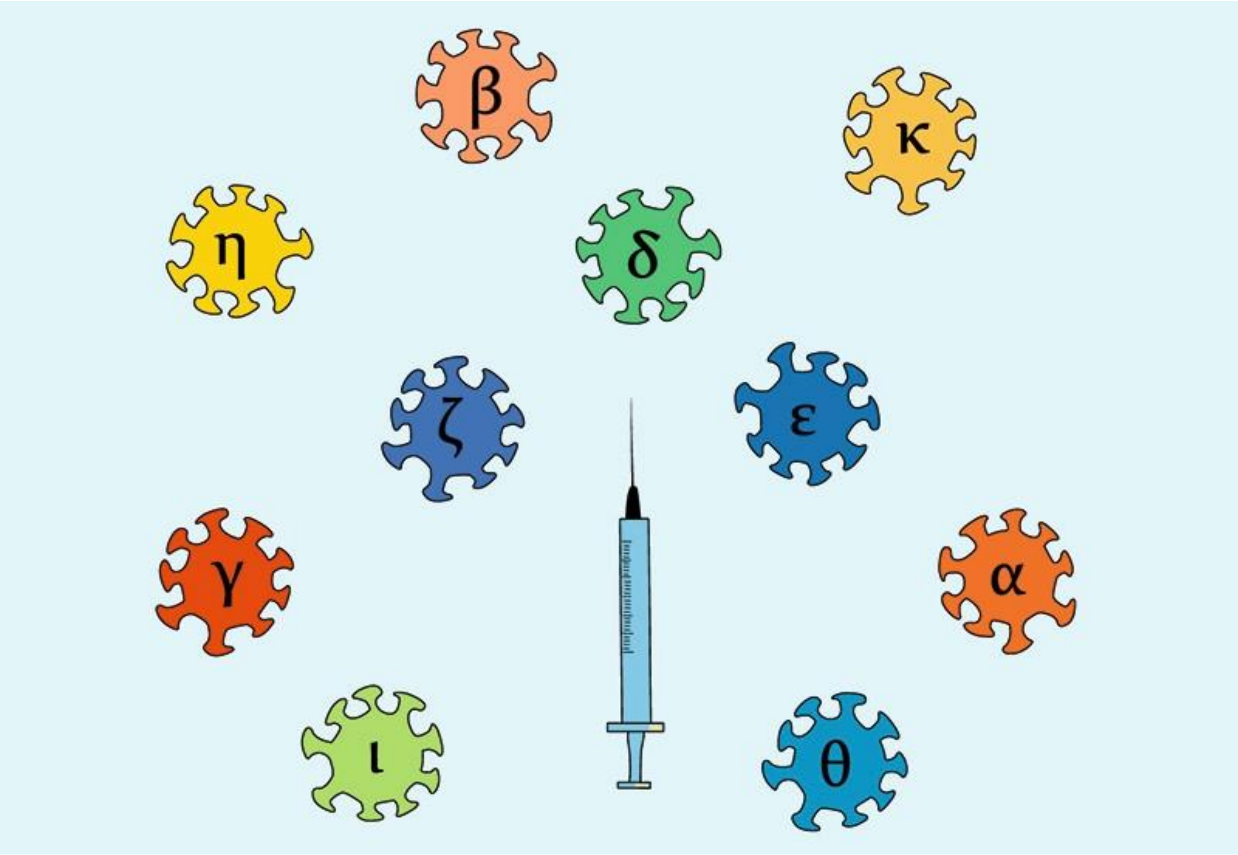
https://www.healthdata.org/covid/covid-19-vaccine-efficacy-summary

Universal Vaccine

NEWS | 19 April 2022

Pan-coronavirus vaccine pipeline takes form

Dozens of 'universal' coronavirus vaccines are in development. But will new technology platforms be able to overcome immunological unknowns?



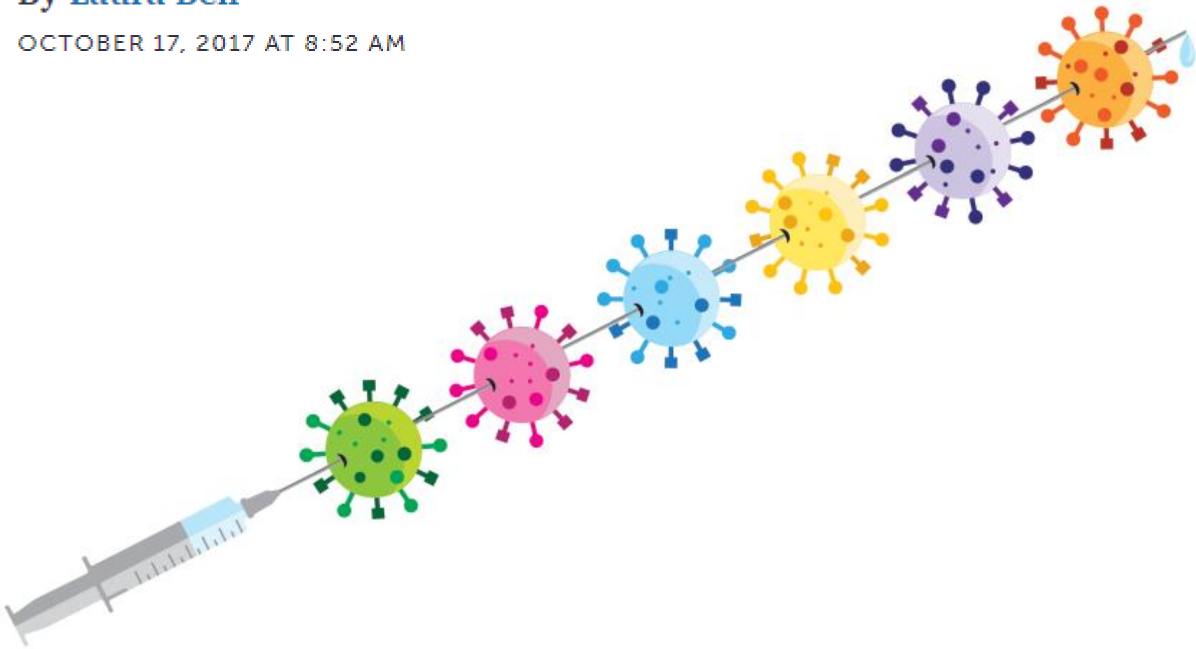
FEATURE HEALTH & MEDICINE

A universal flu shot may be nearing reality

New strategies aim to attack the influenza virus in creative ways

By Laura Beil

OCTOBER 17, 2017 AT 8:52 AM



ScienceNews
INDEPENDENT JOURNALISM SINCE 1921

An urgent Need for Pan-CoV vaccine

The NEW ENGLAND JOURNAL of MEDICINE
Perspective

Universal Coronavirus Vaccines — An Urgent Need

David M. Morens, M.D., Jeffery K. Taubenberger, M.D., Ph.D., and Anthony S. Fauci, M.D.

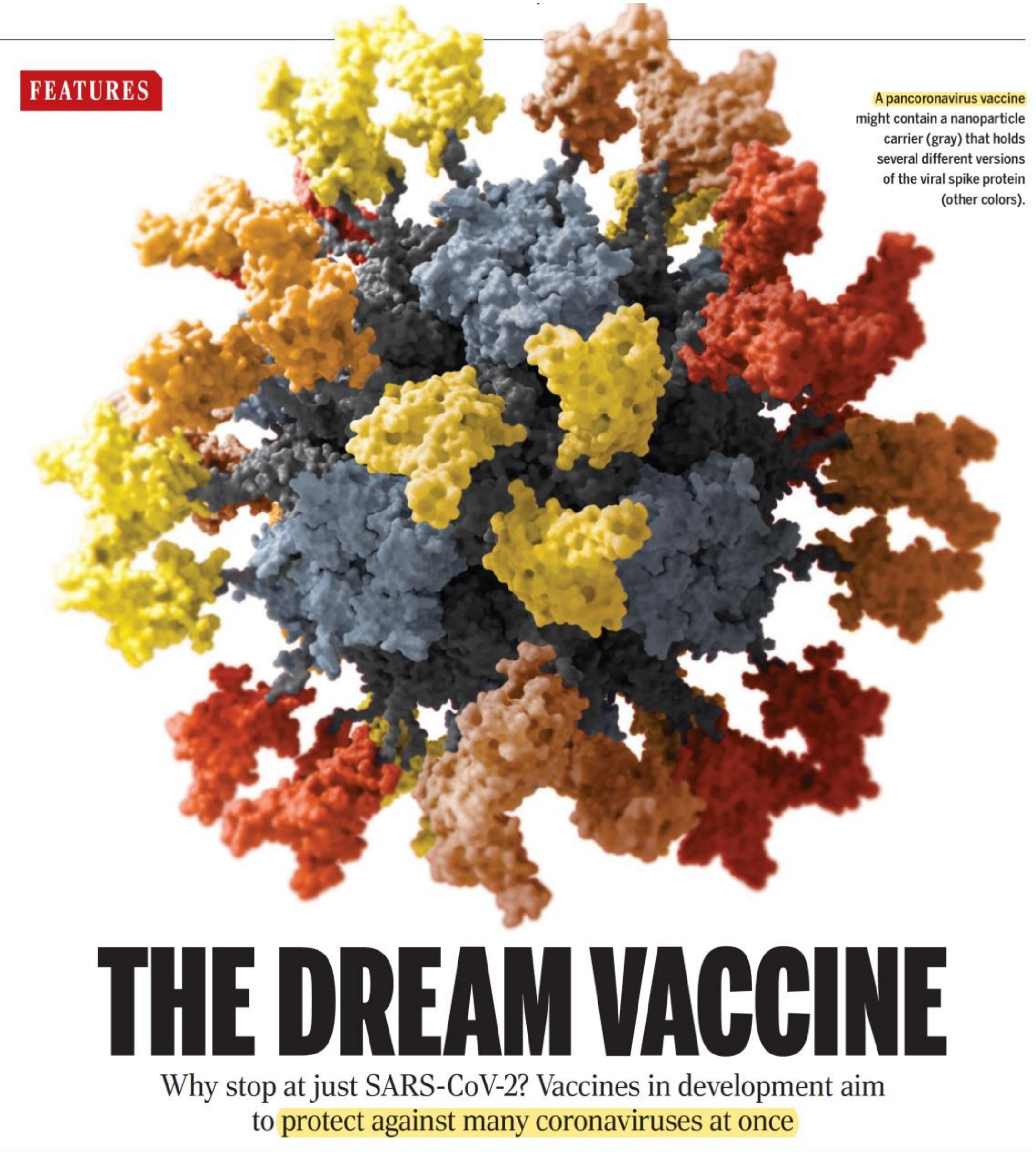
- **목표는 변이주 등장으로 감소된 현재 SARS-CoV-2 백신의 효능을 보완할 수 있는 범용 백신 후보물질을 개발하는 것 뿐 아니라**
- **인류의 미래 판대믹 발생에 대비할 수 있는 광범위한 효능을 가진 백신 후보물질을 사전에 확보하는 것임**

- 변이주 특이적 RBD 또는 spike - mRNA-LNP, 나노입자, ferritin 등.
- 교차 반응을 위해 하나의 플랫폼에 여러 개의 항원 (RBD/스파이크)추가
- RBD 및/또는 S2에 대한 교차 반응성 에피톱 식별 및 **광범위 항체 반응**에 초점을 맞춘 항원 설계
- 비중화항체와 **T세포 반응**을 유도하는 백신 항원 개발

✓ 중저개발 도상국에 대한 (middle or low income countries) 백신 접근성 향상

변이주 및 미래 판데믹을 대비한 범용/ 광범위 백신 필요

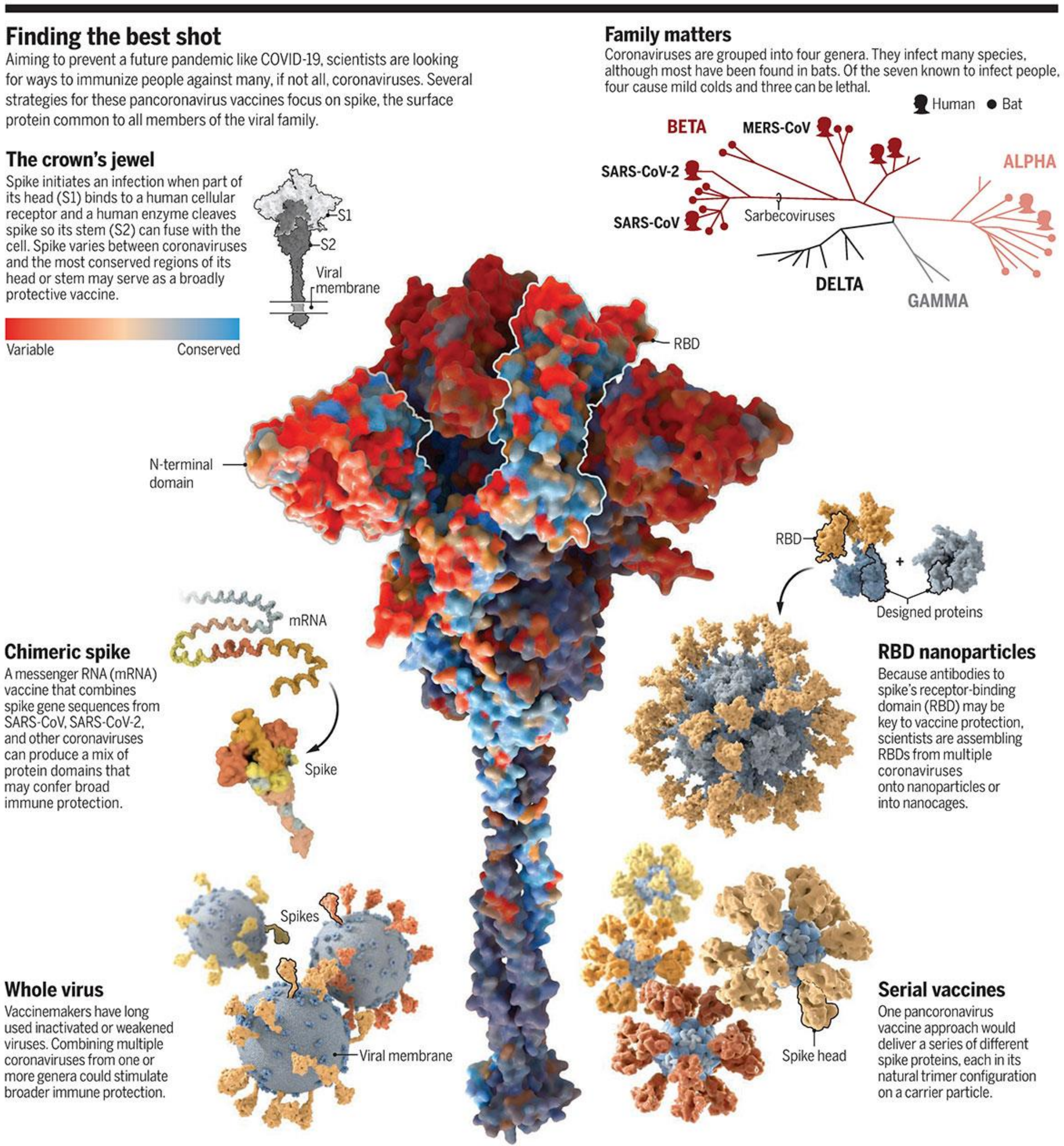
Pan-Coronavirus Vaccines


FEATURES

A pancoronavirus vaccine might contain a nanoparticle carrier (gray) that holds several different versions of the viral spike protein (other colors).

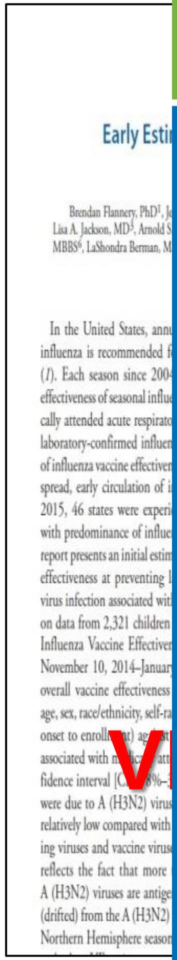
THE DREAM VACCINE

Why stop at just SARS-CoV-2? Vaccines in development aim to protect against many coronaviruses at once

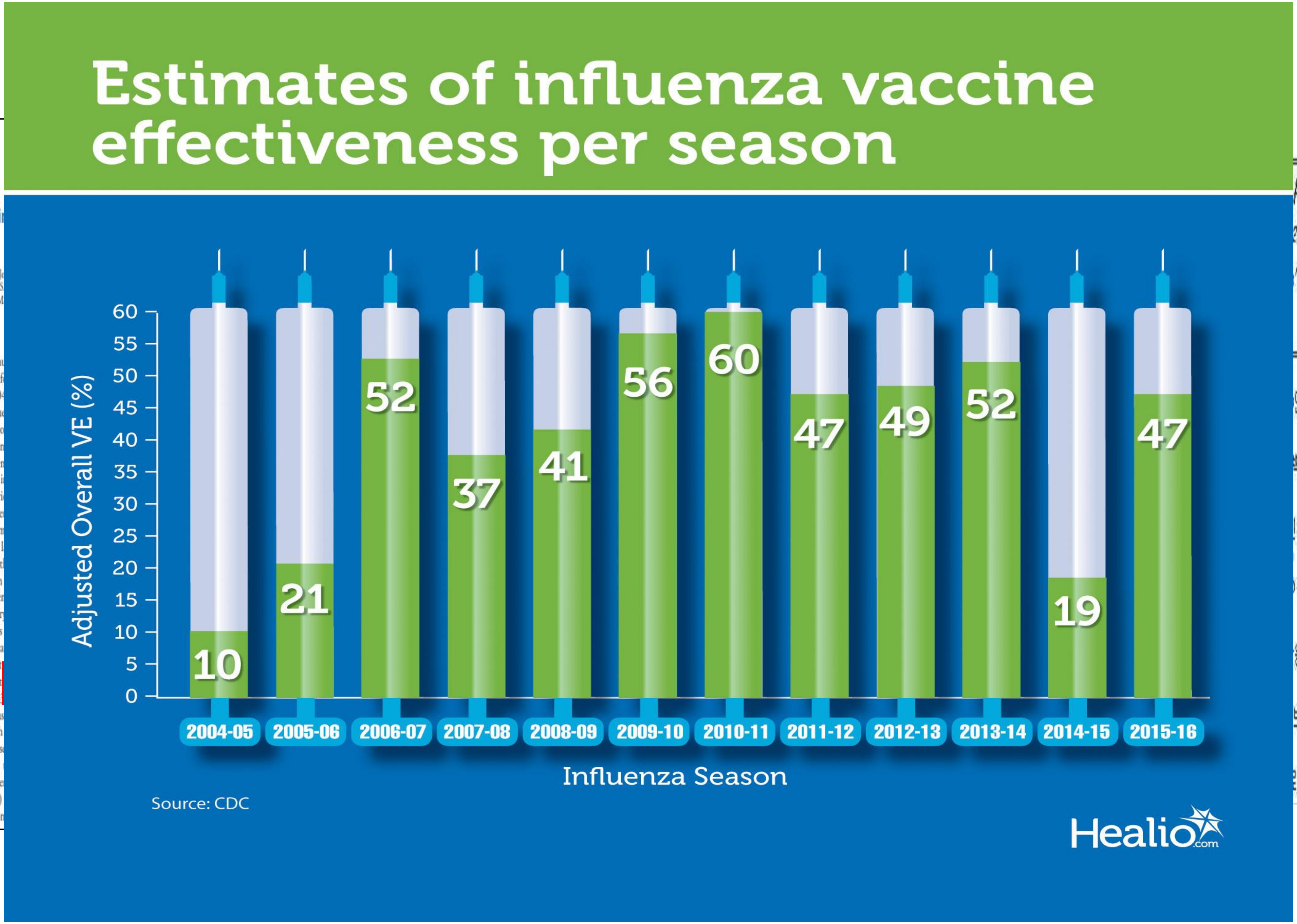


Science, Vol 372, Issue 6539 pp. 227-231, 2021

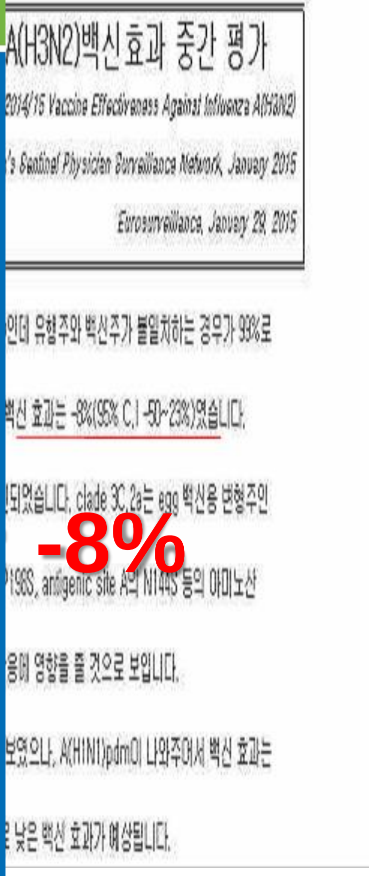
Seasonal Influenza Vaccine Mismatch



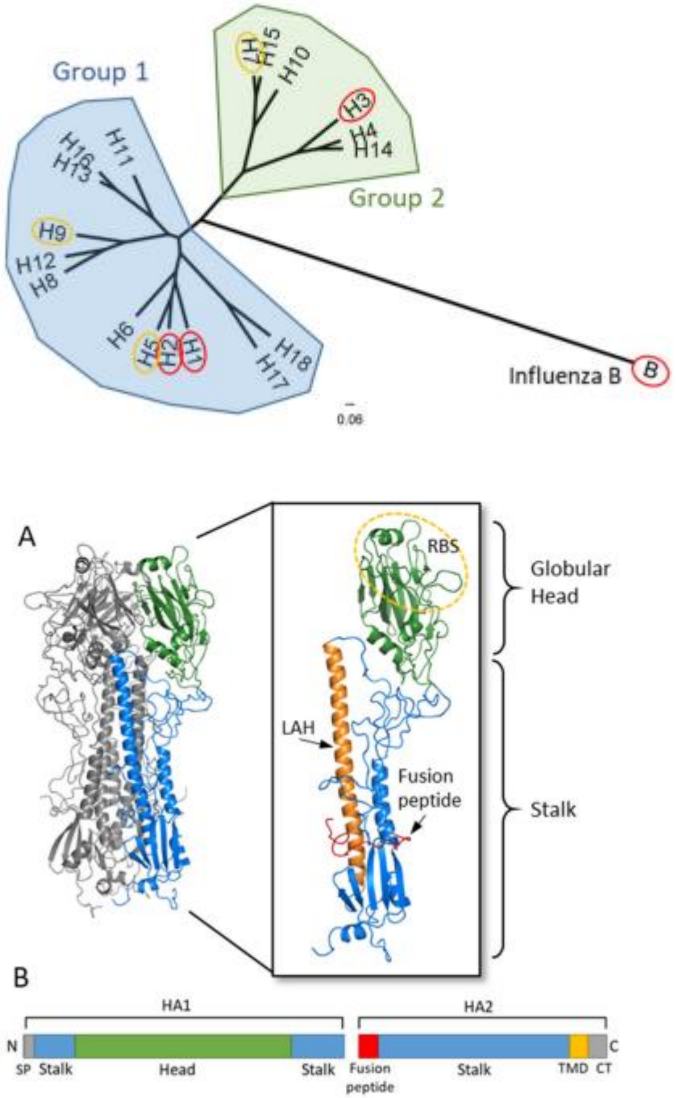
미국, 2014.11.

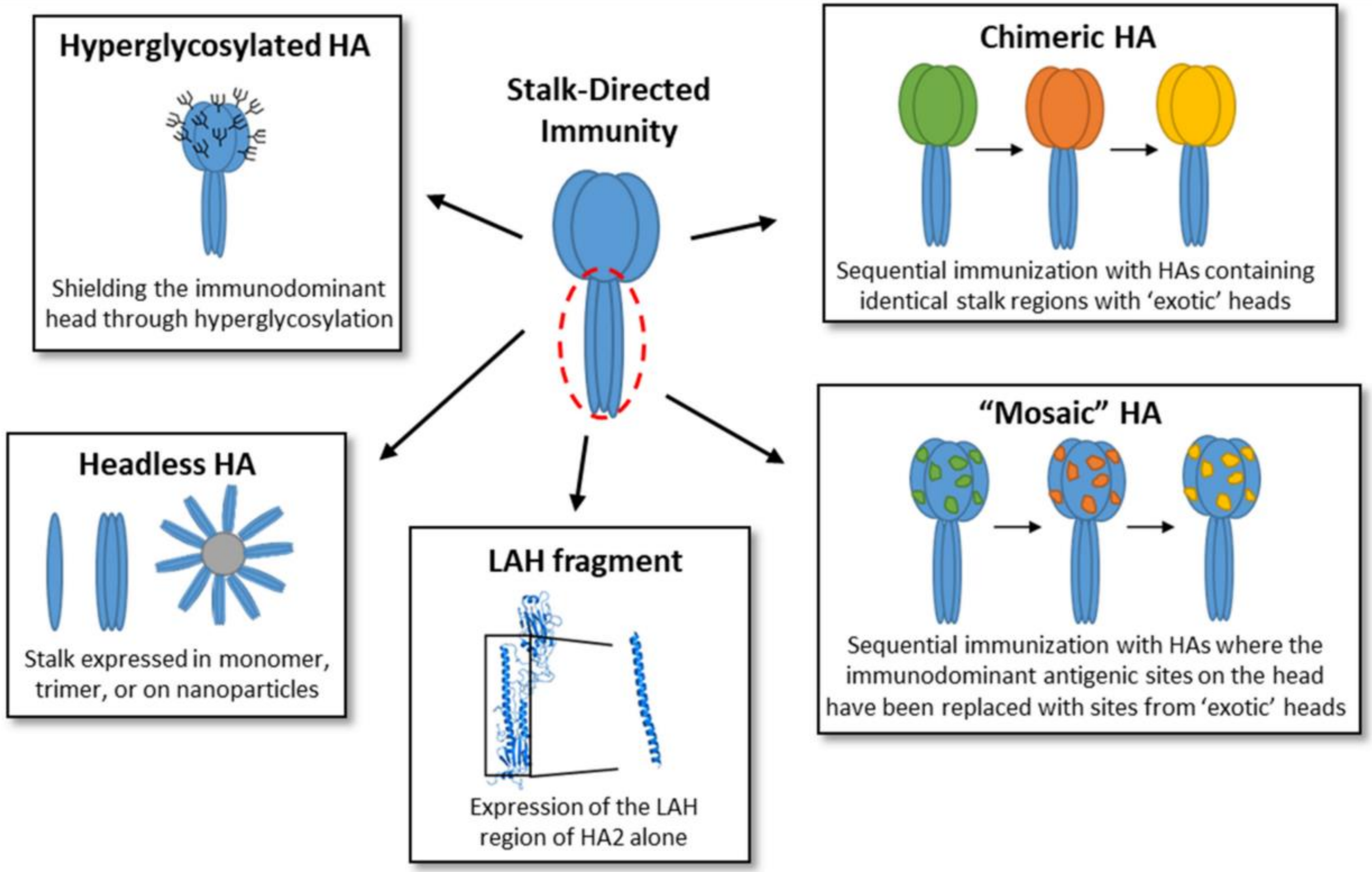


Canada, 2015.1.



HA target UIV strategy (influenza viruses)





Strategies Targeting Hemagglutinin as a Universal Influenza Vaccine. Vaccines 2021, 9, 257.

Ways to go for the UIV

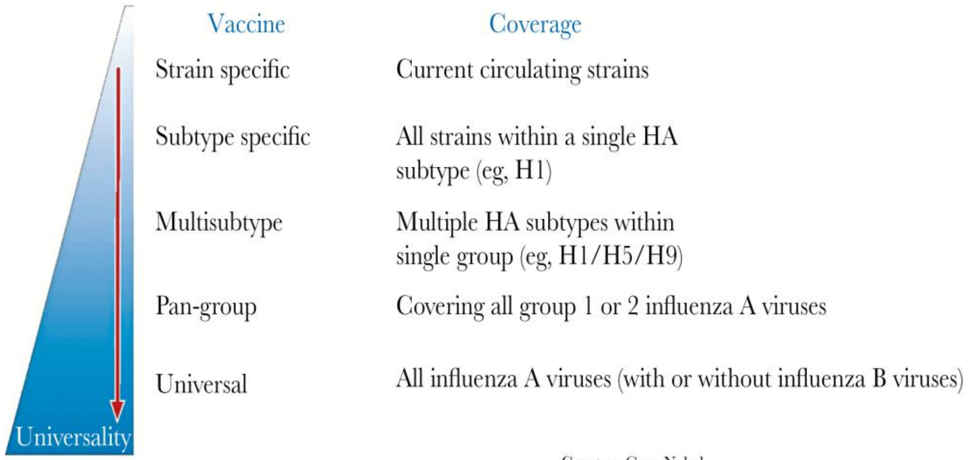
고려대학교 의과대학
Korea University College of Medicine

JOURNAL ARTICLE EDITOR'S CHOICE

A Universal Influenza Vaccine: The Strategic Plan for the National Institute of Allergy and Infectious Diseases FREE

Emily J Erbelding ✉, Diane J Post, Erik J Stemmy, Paul C Roberts, Alison Deckhut Augustine, Stacy Ferguson, Catharine I Paules, Barney S Graham, Anthony S Fauci

The Journal of Infectious Diseases, Volume 218, Issue 3, 1 August 2018, Pages 347–354,
https://doi.org/10.1093/infdis/jiy103



Courtesy Gary Nabel

1. **Improved understanding of influenza <u>transmission, natural history, and pathogenesis</u> of IFNV infection**
   - Anti-HA stem antibodies in prevention of transmission.
   - Role of anti-neuraminidase (NA) antibodies
   - Factors associated with the severity
   - Understanding of antigenic drift and immunodominance
2. **Precisely characterize IFNV <u>immunity and correlates of immune protection</u>**
   - Role of immunologic imprinting and the effect of serial influenza exposure
   - Balance of antibody responses to HA and NA
   - Further understanding of innate and adaptive immune responses that are necessary for protection
   - Vaccine prototypes in the human challenge model
   - Beyond HAI-mediating antibodies
   - Standardize/Harmonize non–HAI-based assays
3. **Support <u>partitional design of UIV</u>**
   - T cell response should be included for antigen design
   - Adjuvants and alternative delivery methods
   - Test promising vaccine platforms/candidates in iterative early Phase for clinical trials

Universal SARS-CoV-2 Vaccine Timelines

Launching unique platform for viral vaccines
- High speed
- LNP
- New delivery methods

Coverage limited to S clade (Wuhan)
- Multi- vaccination
- Reduced VE against Delta

Booster covers several Omicron variants
- BA.4/BA.5 bivalent as booster shot

CMI inducible vaccine Adjustment
- T cell activation regime
- Cross-reactivity & Viral clearance
- Elderly and infants

Universal COVID-19 vaccine
- Protect current Variants
- CMI/ Broadly reactive nAb
- Durability

Pan-Sarbeco vaccine
- True Universality
- Pre-pandemic (Next pandemic)

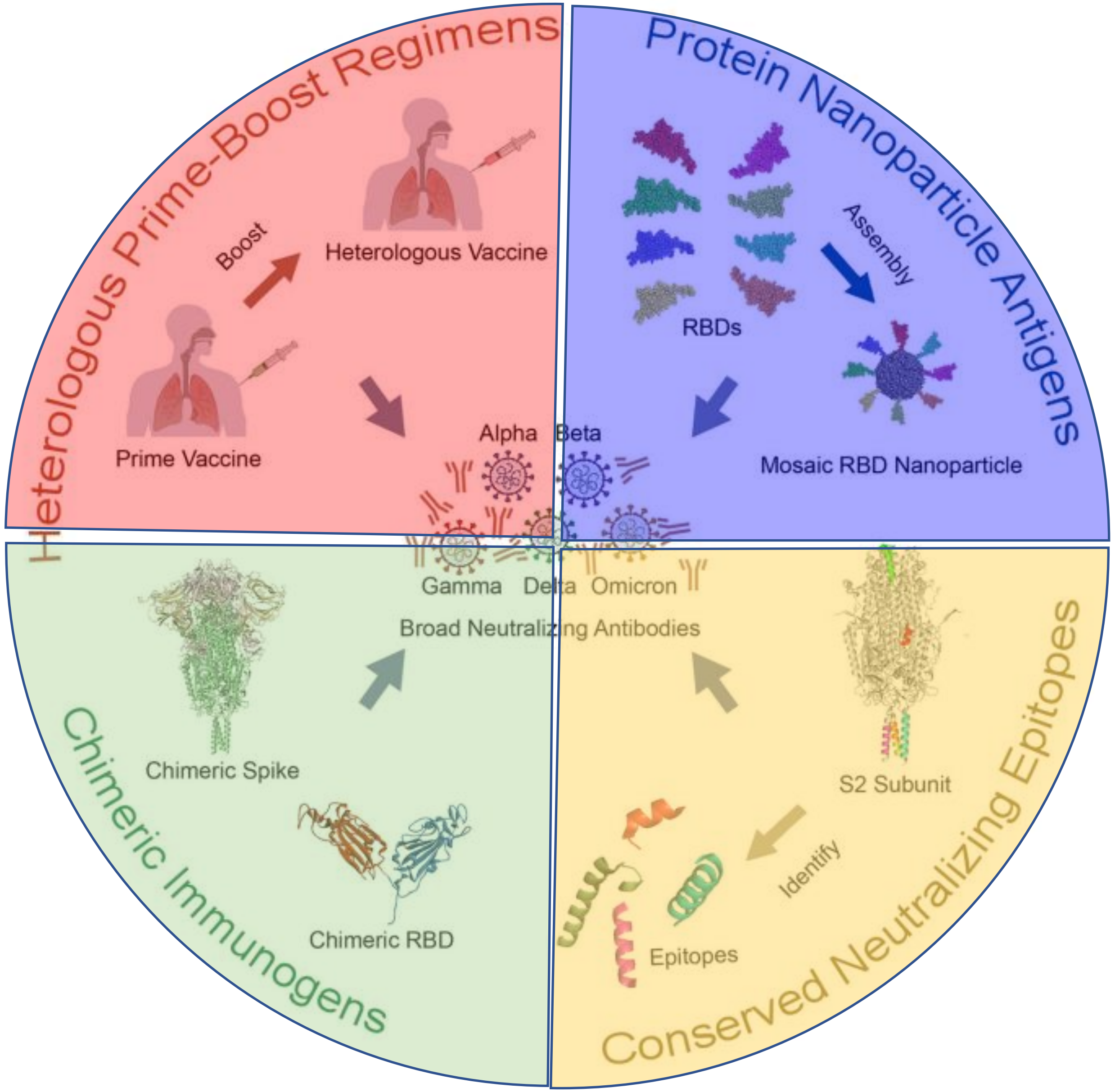
A universal SARS-CoV-2 vaccine should

- be at least 75% sero-protection
- be protective against recent variants as well as zoonotic representative
- have durability up to 6 months
- provide cell-mediated immunity
- be applicable for the next pandemic

Achieved (green),
in-development/not achieved (red)

Four strategies in SARS-CoV-2 universal vaccine design

고려대학교 의과대학
Korea University College of Medicine



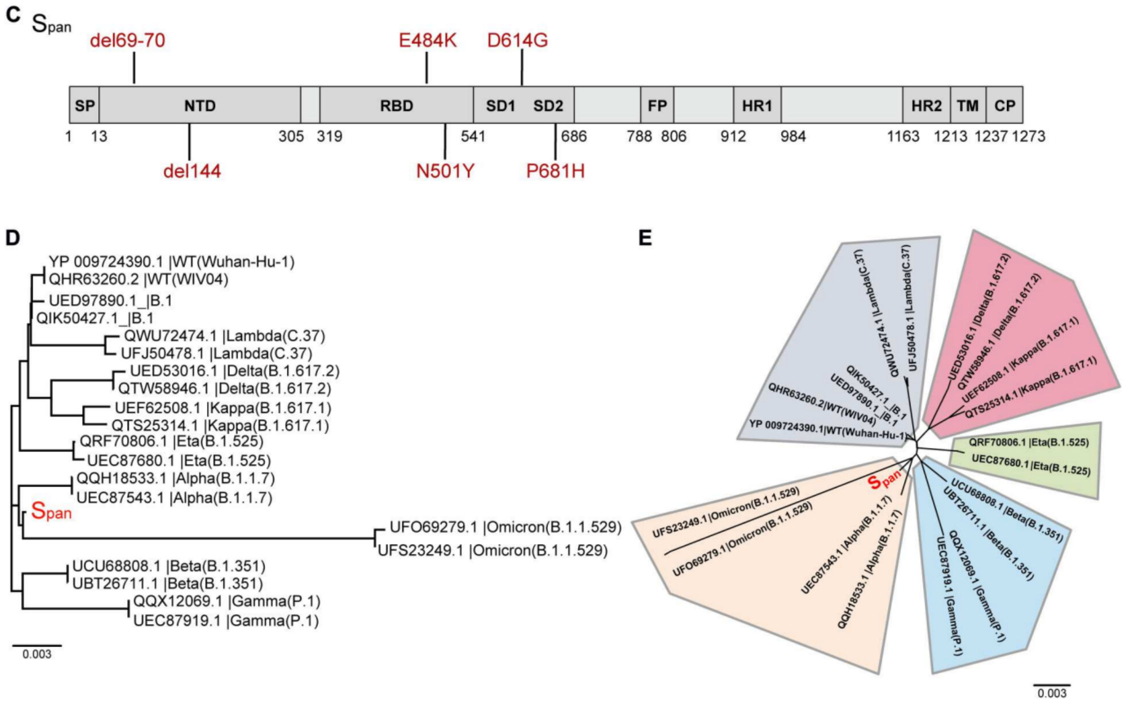
- **Spike Full initially designed by the POMA**
- Optimization with major mutation sites
- Gene construction and cloning into the expression vector
- Mass production of antigens for further study

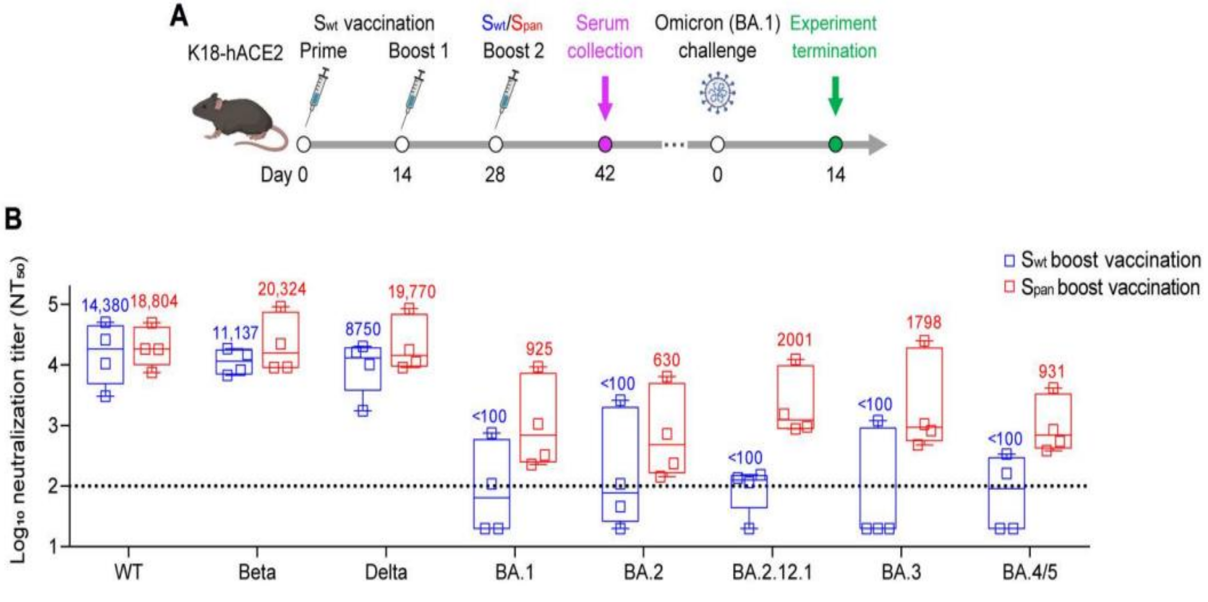
- **Common RBD designed by the POMA**
- Module combination and Selection of tandem sequences
- Gene construction and cloning into the expression vector
- Mass production of antigens for further study

- Selection of appropriate platforms
  - ✓ mRNA
  - ✓ Vector
  - ✓ Recombinant Proteins with adjuvants

- Apply Prime Boost Strategy

npj Vaccines (2022) 7:167 ; https://doi.org/10.1038/s41541-022-00597-4

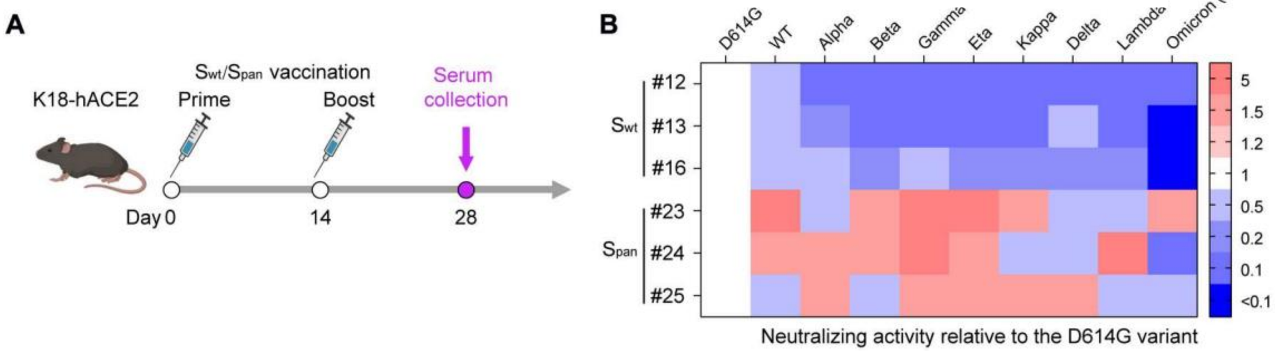




SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CORONAVIRUS

Vaccination with S_{pan}, an antigen guided by SARS-CoV-2 S protein evolution, protects against challenge with viral variants in mice



- **Span** was designed by analyzing the homology of 2675 SARS-CoV-2 S protein sequences from the NCBI database before the Delta variant emerged.
- The refined Span protein harbors high-frequency residues at given positions that reflect cross-clade generality in sequence evolution.
- Span vaccination of mice elicited broad immunity to a wide range of variants
- Vaccinating mice with a heterologous Span booster conferred complete protection against lethal infection with the Omicron variant.

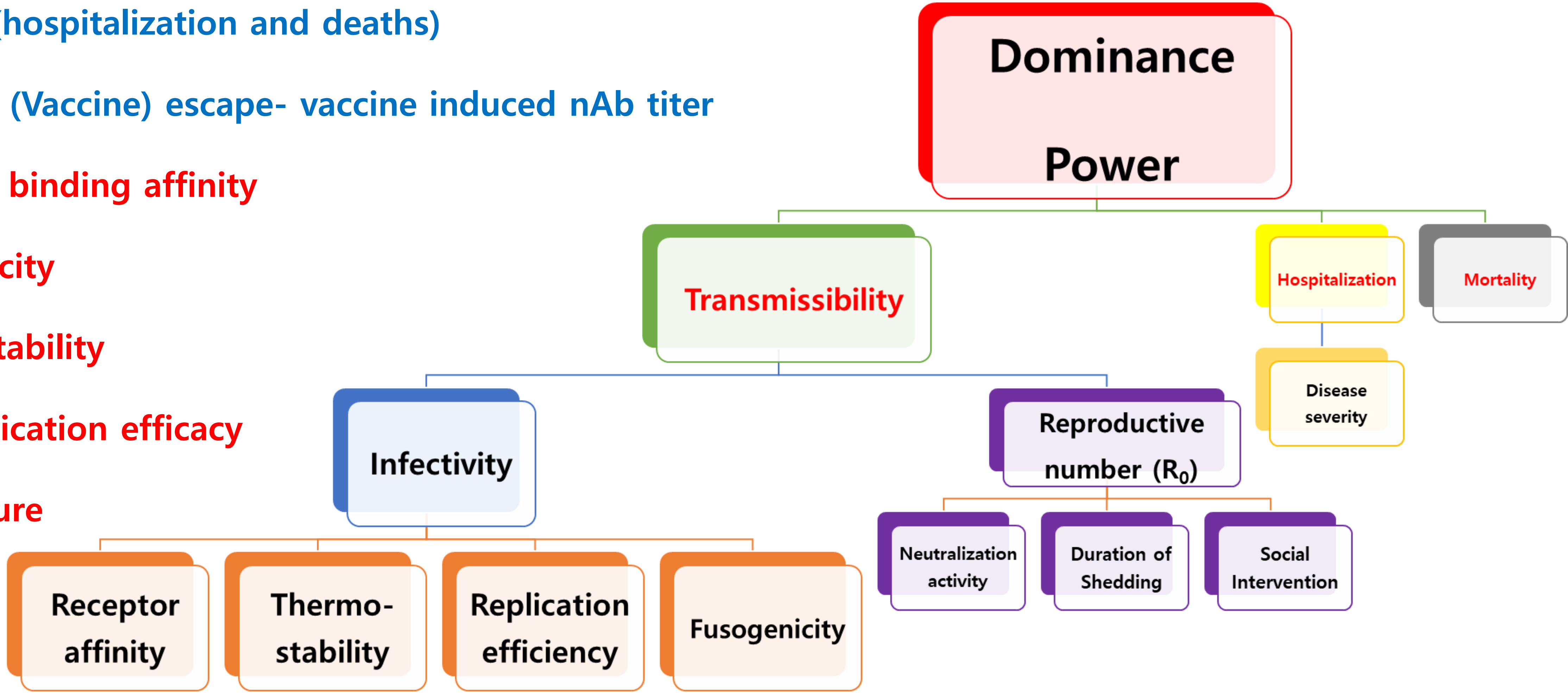
COVID-19 vaccines in current use are disease modifying rather than prevention of infection.

Suggested Criteria for pan-COVID19 Universal vaccine

- Be at least 75% sero-protection, not reduced hospitalization
- Should be protective against recent variant as well as zoonotic representative.
- Have antibody durability up to 6 months.
- Should provide cell-mediated immunity
- Be sure to consider applicability for the next pandemic

Information required for the Risk Assessment of the Variant

- epidemiological situation
- transmissibility including contact tracing data on secondary attack rates, growth rates, Rt and R0
- severity (hospitalization and deaths)
- immune (Vaccine) escape- vaccine induced nAb titer
- Receptor binding affinity
- Fusogenicity
- Thermostability
- RNA replication efficacy
- mAb failure



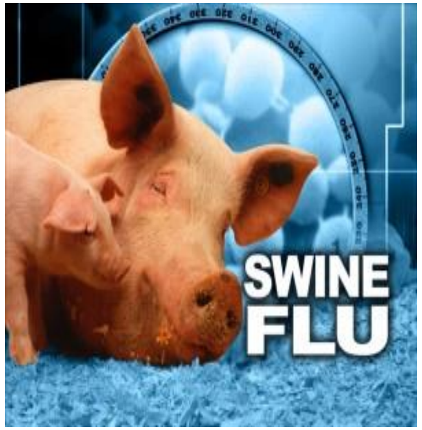
Past Pandemic CANNOT tell about the next one

Credit: US National Museum of Health and Medicine

1918: "Spanish Flu"
A(H1N1)
50 –100 M deaths

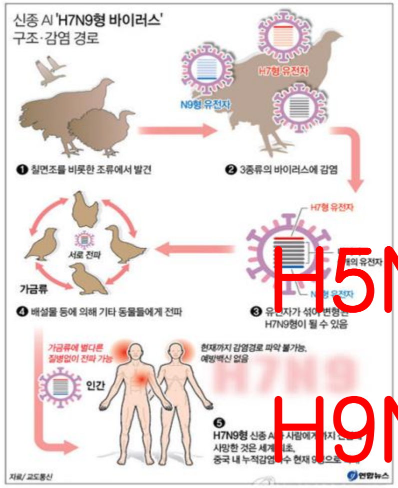
1957: "Asian Flu"
A(H2N2)
1–4 M deaths

1968: "Hong Kong Flu"
A(H3N2)
1–4 M deaths



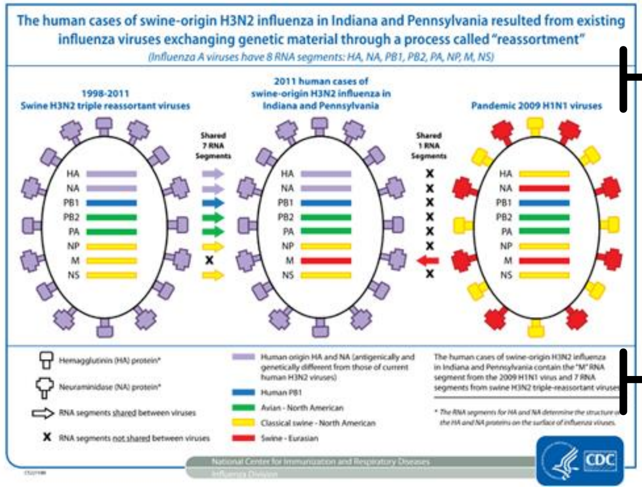
2009: "Pandemic flu"
A(H1N1)
0.1–0.4M deaths
(Lucky case)

What is Next pandemics?



日연구소 "신종 조류독감 H7N9 인간에 감염확인"

H5N6?
H5N1?
H7N9?
H5N8?
H9N2?



H1N2v?

H3N2v?

Isaac B. Weisfuse, NYC Department of Health & Mental Hygiene

Still we do **NOT** know lots of things **under the Sea**

Lets play together with for step-towards !!!!

Acknowledgement

I would like to extend my appreciation to members of the Park's Lab., Dept. of Microbiology, College of Medicine, Korea University

Prof. Man-Seong Park

Prof. Jin Il Kim

Dr. Jong Hyeon Seok

- **Ph.D. candidates**

  Jeonghun Kim

  jae-uk Choi

  Ho Young Lee

- **Supported by**

  The Korea Health Industry Development Institute (Project no. : HV22C0146) and the KCDA (Project no. 2022-ER2403-00)

고려대학교 의과대학
Korea University College of Medicine

VIC-K
고려대학교 의과대학
백신혁신센터

질병관리청
국립보건연구원

GVL Vaccine
글로벌백신기술선도사업단
Global Vaccine Leading Technology Center

NRF 한국연구재단